

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

THIS PAGE BLANK (USPTO)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 September 2003 (18.09.2003)

PCT

(10) International Publication Number
WO 03/076427 A1

(51) International Patent Classification⁷: **C07D 401/04**,
471/04, 487/04, A61K 31/517, A61P 9/12

(21) International Application Number: PCT/IB03/00998

(22) International Filing Date: 5 March 2003 (05.03.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0206033.3 14 March 2002 (14.03.2002) GB

(71) Applicant (for GB only): **PFIZER LIMITED** [GB/GB];
Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

Mark, Henryk [GB/GB]; Pfizer Central Research and development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). **STOBIE, Alan** [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(74) Agents: **HAYLES, James, R.** et al.; Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(71) Applicant (for all designated States except GB, US): **PFIZER INC.** [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BLAGG, Julian** [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). **FRAY, Michael, Jonathan** [GB/GB]; Pfizer Central Research and development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). **LEWIS, Mark, Llewellyn** [GB/GB]; Pfizer Central Research and development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). **MATHIAS, John, Paul** [GB/GB]; Pfizer Central Research and development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). **STEFANIAK,**

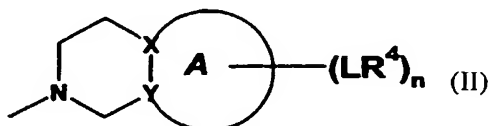
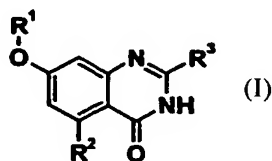
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: QUINAZOLINE COMPOUNDS USEFUL IN THERAPY



(57) Abstract: Compounds of formula (I): or pharmaceutically acceptable salts or solvates thereof, wherein R¹ represents C₁₋₄ alkyl; R² represents halo, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkoxy, -SO₂(C₁₋₄ alkyl), optionally substituted C₁₋₄ alkyloxy, Het or

-OHet; R³ represents a bicyclic group of the formula wherein X and Y are selected from C and N, provided that at least one is C; Ring A together with X and Y represents a 5- or 6-membered aromatic, ring containing 0, 1, 2 or 3 nitrogen atoms in the ring; n is 1 or 2; L represents a direct link, C₁₋₄ alkylene or C₁₋₄ alkoxyalkylene; R⁴ represents H, -NR⁵R⁶, C₃₋₆ cycloalkyl, -OR⁷, Het¹ or Het²; R⁵ and R⁶ are independently selected from H, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyl-C₁₋₄ alkylene, -SO₂(C₁₋₄ alkyl) and optionally substituted C₁₋₄ alkyl. R⁷ is selected from H, C₁₋₄ alkyl, C₁₋₄ alkoxyalkyl, C₃₋₆ cycloalkyl, Het² and C₁₋₄ alkyl-Het³; R⁸ is H or C₁₋₄ alkyl; Het¹, Het² and Het³ independently represent an optionally substituted 4 to 7 membered saturated heterocyclic group which may be mono- or bi-cyclic and which contains one or more heteroatoms selected from N, O or S; Het⁴ represents an optionally substituted 5 or 6 membered unsaturated heterocyclic group containing one or more heteroatoms selected from N, O or S; R⁹ is H or C₁₋₄ alkyl; R¹⁰ and R¹¹ are independently selected from H and C₁₋₄ alkyl; are useful in the treatment of hypertension, myocardial infarction, male erectile dysfunction (MED), hyperlipidaemia, cardiac arrhythmia, glaucoma and benign prostatic hyperplasia (BPH). They also find utility in the treatment of female sexual arousal dysfunction (FSAD).

QUINAZOLINE COMPOUNDS USEFUL IN THERAPY

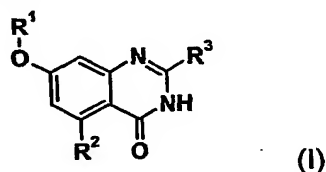
This invention relates to novel compounds useful in therapy. It also relates to compositions containing such derivatives and to their use. They have potential utility in the treatment of hypertension, myocardial infarction, male erectile dysfunction (MED), hyperlipidaemia, cardiac arrhythmia, glaucoma and benign prostatic hyperplasia (BPH). They also may be useful in the treatment of female sexual arousal dysfunction (FSAD).

International Patent Application WO 97/23462 discloses quinoline and quinazoline compounds having a 5-phenyl substituent. The compounds are indicated in the treatment of benign prostatic hyperplasia.

International Patent application WO 98/30560 discloses quinoline and quinazoline compounds indicated in the treatment of benign prostatic hyperplasia.

International Patent application WO02/053558 (published after the priority date of this application) discloses quinazoline derivatives indicated in the treatment of benign prostatic hyperplasia.

According to the present invention, there are provided compounds of the formula (I):

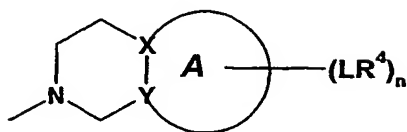


and pharmaceutically acceptable salts or solvates thereof, wherein

R¹ represents C₁₋₄ alkyl;

R² represents halo, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyloxy, -SO₂(C₁₋₄ alkyl), C₁₋₄ alkyloxy (optionally substituted by C₃₋₆ cycloalkyl or C₁₋₄ alkoxy), Het or -OHet;

R³ represents a bicyclic group of the formula



wherein X and Y are selected from C and N, provided that at least one is C;

Ring A together with X and Y represents a 5- or 6-membered aromatic ring
5 containing 0, 1, 2 or 3 nitrogen atoms in the ring;

n is 0, 1 or 2

L independently represents a direct link, C₁₋₄ alkylene or C₁₋₄ alkoxyalkylene;
10

R⁴ independently represents H, -NR⁵R⁶, C₃₋₆ cycloalkyl, -OR⁷, Het¹ or Het⁴;

R⁵ and R⁶ are independently selected from H, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyl-C₁₋₄
alkylene, -SO₂(C₁₋₄ alkyl) and C₁₋₄ alkyl (optionally substituted with -OR⁸, -NR¹⁰R¹¹, Het¹
15 or Het⁴);

R⁷ is selected from H, C₁₋₄ alkyl, C₁₋₄ alkoxyalkyl, C₃₋₆cycloalkyl, Het² and
C₁₋₄alkyl-Het³;

20 R⁸ is H or C₁₋₄ alkyl;

Het, Het¹, Het² and Het³ independently represent a 4 to 7 membered saturated
heterocyclic group which may be mono- or bi-cyclic and which contains one or more
heteroatoms selected from N, O or S, optionally substituted with OR⁹ and/or C₁₋₄ alkyl
25 optionally substituted by OR⁹;

Het⁴ represents a 5 or 6 membered unsaturated heterocyclic group containing
one or more heteroatoms selected from N, O or S, optionally substituted with C₁₋₄ alkyl;

30 R⁹ is H or C₁₋₄ alkyl;

R¹⁰ and R¹¹ are independently selected from H and C₁₋₄ alkyl.

In the above definitions alkyl, alkoxy and cycloalkyl groups containing the requisite number of carbon atoms, except where indicated, can be unbranched- or branched-chain. Examples of alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. Examples of alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy and t-butoxy. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Unless otherwise provided herein:

WSCDI means 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride;

10 DCC means N,N'-dicyclohexylcarbodiimide;
HOAT means 1-hydroxy-7-azabenzotriazole;
HOBT means 1-hydroxybenzotriazole hydrate;
PyBOP® means Benzotriazol-1-yloxytris(pyrrolidino)phosphonium
hexafluorophosphate;

15 PyBrOP® means bromo-tris-pyrrolidino-phosphonium hexafluorophosphate;
Mukaiyama's reagent means 2-chloro-1-methylpyridinium iodide;
KHMDs means potassium bis(trimethylsilyl)amide;
Hünig's base means N-ethyldiisopropylamine;
Et₃N means triethylamine;

20 NMM means N-methylmorpholine;
DEAD means diethyl azodicarboxylate;
DIAD means diisopropyl azodicarboxylate;
DIBAL-H means diisobutylaluminium hydride;
BINAP means 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl;

25 DBA means dibenzylideneacetone;
Boc means *tert*-butoxycarbonyl;
CBz means benzyloxycarbonyl;
(Boc)₂O means di-*tert*-butyl dicarbonate;
MeOH means methanol, EtOH means ethanol, and EtOAc means ethyl acetate;

30 THF means tetrahydrofuran, DMSO means dimethyl sulphoxide, and DCM
means dichloromethane;
AcOH means acetic acid, TFA means trifluoroacetic acid;
TFAA means trifluoroacetic anhydride and NMMO means 4-methylmorpholine
N-oxide monohydrate.

35

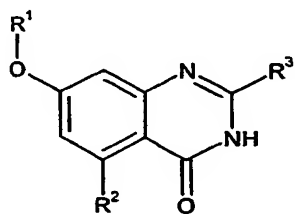
The pharmaceutically acceptable salts of the compounds of the formula (I) include the acid addition and base salts thereof. Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, *p*-toluenesulphonate and palmoate salts.

Suitable base salts are formed from bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc and diethanolamine salts. For a review on suitable salts see Berge et al, J. Pharm. Sci, 66, 1-19, 1977.

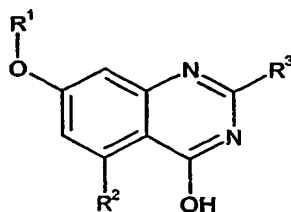
The pharmaceutically acceptable solvates of the compounds of the formula (I) or salts thereof include the hydrates thereof.

Also included within the present scope of the compounds of the formula (I) are polymorphs thereof.

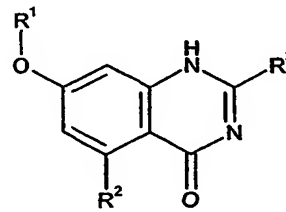
A compound of the formula (I) may contain one or more asymmetric carbon atoms and therefore exist in two or more stereoisomeric forms. The present invention includes the individual stereoisomers of the compounds of formula (I) along with the individual tautomeric forms (1a, 1b and 1c) thereof, together with mixtures thereof.



1a



1b



1c

Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of the formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of the formula (I) may also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of

the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

The present invention also includes all suitable isotopic variations of a compound of the formula (I) or a pharmaceutically acceptable salt thereof. An isotopic variation of a compound of the formula (I) or a pharmaceutically acceptable salt thereof is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that can be incorporated into compounds of the formula (I) and pharmaceutically acceptable salts thereof include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine and chlorine such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl , respectively. Certain isotopic variations of the compounds of the formula (I) and pharmaceutically acceptable salts thereof, for example, those in which a radioactive isotope such as ^3H or ^{14}C is incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated, i.e. ^3H , and carbon-14, i.e. ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium, i.e. ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of the compounds of formula (I) and pharmaceutically acceptable salts thereof of this invention can generally be prepared by conventional procedures such as by the illustrative methods or by the preparations described in the Examples and Preparations hereafter using appropriate isotopic variations of suitable reagents.

Preferred groups of compounds that may be mentioned include those in which:

Het¹, Het² and Het³ contain at least one N atom and are linked to L through an N atom.

More preferred groups of compounds include those in which:

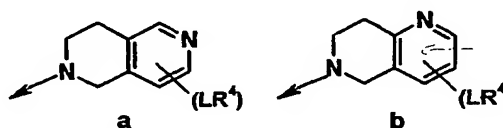
Het¹, Het² and Het³ include azetidine, pyrrolidine, piperidine, piperazine, azepane, morpholine, homomorpholine, or one of the following ring systems:



optionally substituted by OR^9 and/or C_{1-4} alkyl optionally substituted by OR^9 .

Still more preferred groups of compounds that may be mentioned include those in which:

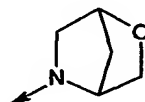
- 5 (a) R^1 is CH_3 ;
 (b) R^2 is cyclopropyl;
 (c) L is methylene;
 (d) R^3 represents a group chosen from a or b (bonded to the quinazolinone through the N-atom as indicated)



10

where LR^4 is CH_2Het^1 or $\text{CH}_2\text{NR}^5\text{R}^6$ and Het^1 , R^5 and R^6 are as hereinbefore defined;

- (e) Het^1 represents an N-linked morpholinyl
 (f) R^5 and R^6 are independently selected from H or C_{1-3} alkyl optionally substituted by OCH_3 ;
 15 (g) Het^1 , Het^2 and Het^3 are selected from the group comprising pyrrolidine, piperidine, morpholine or



- 20 Compounds that may be prepared according to the invention, amongst others, are:

5-cyclopropyl-7-methoxy-2-(2-(4-methoxypiperidin-1-ylmethyl)-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(2-([dimethylamino]methyl)-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone;

- 25 5-cyclopropyl-7-methoxy-2-(2-(1-pyrrolidinylmethyl)-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone;

5-cyclopropyl-7-methoxy-2-(2-(4-morpholinylmethyl)-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone;

- 30 5-cyclopropyl-7-methoxy-2-(5-([dimethylamino]methyl)-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone;

- 5-cyclopropyl-7-methoxy-2-(5-(1-pyrrolidinylmethyl)-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone;
- 5-cyclopropyl-7-methoxy-2-(5-(1-piperidinylmethyl)-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone;
- 5 5-cyclopropyl-7-methoxy-2-(5-(4-morpholinylmethyl)-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone;
- 5-cyclopropyl-7-methoxy-2-(5-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone;
- 5-cyclopropyl-7-methoxy-2-(2-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone;
- 10 5-cyclopropyl-7-methoxy-2-[3-(morpholin-4-ylmethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl]-4(3H)-4(3H)-quinazolinone;
- 5-cyclopropyl-2-[3-(hydroxymethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl]-7-methoxy-4(3H)-quinazolinone;
- 15 5-cyclopropyl-7-methoxy-2-[3-(4-methoxypiperidin-1-yl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl]-4(3H)-quinazolinone;
- 5-cyclobutyl-7-methoxy-2-[2-(morpholin-4-ylmethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl]-4(3H)-quinazolinone;
- 2-(7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5-isopropyl-7-methoxy-4(3H)-quinazolinone;
- 20 5-isopropyl-7-methoxy-2-[5-(morpholin-4-ylmethyl)-3,4-dihydroiso-4(3H)-quinolin-2(1H)-yl]-4(3H)-quinazolinone;
- 5-isopropyl-7-methoxy-2-[2-[(pyridin-2-ylmethyl)amino]-7,8-dihydro-1,6-naphthyridin-6(5H)-yl]-4(3H)-quinazolinone;
- 25 *N*-{2-[5-(cyclobutyloxy)-7-methoxy-4-oxo-3,4-dihydro-2-quinazolinyl]-1,2,3,4-tetrahydro-5-iso-4(3H)-quinolinyl}methanesulfonamide;
- 2-(7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5-isopropoxy-7-methoxy-4(3H)-quinazolinone;
- 5-isopropoxy-7-methoxy-2-[2-[(2-methoxyethyl)amino]-7,8-dihydro-1,6-naphthyridin-6(5H)-yl]-4(3H)-quinazolinone;
- 30 5-(cyclobutyloxy)-2-[5-[(diethylamino)methyl]-3,4-dihydroiso-4(3H)-quinolin-2(1H)-yl]-7-methoxy-4(3H)-quinazolinone;
- 2-(7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-7-methoxy-5-(tetrahydrofuran-3-yloxy)-4(3H)-quinazolinone;

7-methoxy-2-[2-[(2-methoxyethyl)amino]-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl]-5-(tetrahydrofuran-3-yloxy)-4(3*H*)-quinazolinone;

7-methoxy-2-[2-[(pyridin-2-ylmethyl)amino]-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl]-5-(tetrahydrofuran-3-yloxy)-4(3*H*)-quinazolinone;

5 2-(7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)-7-methoxy-5-(2-methoxyethoxy)-4(3*H*)-quinazolinone;

7-methoxy-5-(2-methoxyethoxy)-2-[5-[(pyridin-2-ylmethyl)amino]-3,4-dihydro-2,6-naphthyridin-2(1*H*)-yl]-4(3*H*)-quinazolinone;

10 7-methoxy-5-(2-methoxyethoxy)-2-[2-[(2-methoxyethyl)amino]-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl]-4(3*H*)-quinazolinone;

7-methoxy-5-(2-methoxyethoxy)-2-[2-[(pyridin-2-ylmethyl)amino]-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl]-4(3*H*)-quinazolinone;

5-(cyclopropylmethoxy)-2-(7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)-7-methoxy-4(3*H*)-quinazolinone;

15 5-(cyclopropylmethoxy)-7-methoxy-2-[5-[(pyridin-2-ylmethyl)amino]-3,4-dihydro-2,6-naphthyridin-2(1*H*)-yl]-4(3*H*)-quinazolinone;

5-(cyclopropylmethoxy)-7-methoxy-2-[2-[(pyridin-2-ylmethyl)amino]-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl]-4(3*H*)-quinazolinone;

20 5-isopropoxy-7-methoxy-2-[2-[(pyridin-2-ylmethyl)amino]-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl]-4(3*H*)-quinazolinone;

5-cyclopropyl-7-methoxy-2-[5-[(3*R*)-1-methylpyrrolidin-3-yl]oxy]-3,4-dihydroiso-4(3*H*)-quinolin-2(1*H*)-yl]-4(3*H*)-quinazolinone;

5-cyclopropyl-7-methoxy-2-[5-[(3*S*)-1-methylpyrrolidin-3-yl]oxy]-3,4-dihydroiso-4(3*H*)-quinolin-2(1*H*)-yl]-4(3*H*)-quinazolinone;

25 5-cyclopropyl-7-methoxy-2-[5-[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]-3,4-dihydroiso-4(3*H*)-quinolin-2(1*H*)-yl]-4(3*H*)-quinazolinone;

5-cyclopropyl-7-methoxy-2-[5-[(2*R*)-1-methylpyrrolidin-2-yl]methoxy]-3,4-dihydroiso-4(3*H*)-quinolin-2(1*H*)-yl]-4(3*H*)-quinazolinone;

30 5-cyclopropyl-7-methoxy-2-(2-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)-4(3*H*)-quinazolinone;

5-cyclopropyl-7-methoxy-2-[2-(1-methylpiperidin-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl]-4(3*H*)-quinazolinone;

5-cyclopropyl-2-[2-[(2-hydroxyethyl)amino]methyl]-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl]-7-methoxy-4(3*H*)-quinazolinone;

- 5-cyclopropyl-7-methoxy-2-[2-[(2-methoxyethyl)(methyl)amino]methyl]-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl]-4(3*H*)-quinazolinone;
- 5-cyclopropyl-7-methoxy-2-[5-[(3-methoxyazetidin-1-yl)methyl]-3,4-dihydro-2,6-naphthyridin-2(1*H*)-yl]-4(3*H*)-quinazolinone;
- 5 5-cyclopropyl-7-methoxy-2-[5-[(3*S*)-3-methoxypyrrolidin-1-yl)methyl]-3,4-dihydro-2,6-naphthyridin-2(1*H*)-yl]-4(3*H*)-quinazolinone;
- 5-cyclopropyl-7-methoxy-2-[5-[(1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]-3,4-dihydro-2,6-naphthyridin-2(1*H*)-yl]-4(3*H*)-quinazolinone;
- 5-cyclopropyl-7-methoxy-2-[2-[[[(1*S*)-2-methoxy-1-methylethyl](methyl)amino]methyl]-7,8-dihydropyrido[4,3-*d*]pyrimidin-6(5*H*)-yl]-4(3*H*)-quinazolinone;
- 10 5-cyclopropyl-7-methoxy-2-[2-[(4-methoxypiperidin-1-yl)methyl]-7,8-dihydropyrido[4,3-*d*]pyrimidin-6(5*H*)-yl]-4(3*H*)-quinazolinone;
- 5-cyclopropyl-2-[3-(cyclopropylmethyl)-5,6-dihydroimidazo[1,5-*a*]pyrazin-7(8*H*)-yl]-7-methoxy-4(3*H*)-quinazolinone;
- 15 5-cyclopropyl-7-methoxy-2-(3-morpholin-4-yl-5,6-dihydroimidazo[1,5-*a*]pyrazin-7(8*H*)-yl)-4(3*H*)-quinazolinone;
- 5-cyclopropyl-7-methoxy-2-[2-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl]-4(3*H*)-quinazolinone;
- 20 5-cyclohexyl-7-methoxy-2-[2-(morpholin-4-ylmethyl)-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl]-4(3*H*)-quinazolinone;
- 5-isopropyl-7-methoxy-2-[2-[(2-methoxyethyl)amino]-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl]-4(3*H*)-quinazolinone;
- 5-isopropyl-7-methoxy-2-[5-(morpholin-4-ylmethyl)-3,4-dihydro-2,6-naphthyridin-2(1*H*)-yl]-4(3*H*)-quinazolinone dihydrochloride;
- 25 5-isopropyl-7-methoxy-2-[5-[(2-methoxyethyl)(methyl)amino]methyl]-3,4-dihydro-2,6-naphthyridin-2(1*H*)-yl]-4(3*H*)-quinazolinone dihydrochloride;
- 5-isopropyl-7-methoxy-2-[2-(pyrrolidin-1-ylmethyl)-7,8-dihydropyrido[4,3-*d*]pyrimidin-6(5*H*)-yl]-4(3*H*)-quinazolinone dihydrochloride;
- 30 2-(5-amino-3,4-dihydro-2,6-naphthyridin-2(1*H*)-yl)-5-isopropyl-7-methoxy-4(3*H*)-quinazolinone dihydrochloride;
- 2-[4-amino-2-[(2-methoxyethyl)amino]-7,8-dihydropyrido[4,3-*d*]pyrimidin-6(5*H*)-yl]-5-isopropyl-7-methoxy-4(3*H*)-quinazolinone dihydrochloride;
- 5-isopropyl-7-methoxy-2-[2-(methylamino)-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl]-4(3*H*)-quinazolinone dihydrochloride;
- 35

2-[4-[ethyl(methyl)amino]-5,8-dihydropyrido[3,4-*d*]pyrimidin-7(6*H*)-yl]-5-isopropyl-7-methoxy-4(3*H*)-quinazolinone dihydrochloride;

5-isopropyl-7-methoxy-2-[5-[(3-methoxyazetidin-1-yl)methyl]-3,4-dihydroiso-4(3*H*)-quinolin-2(1*H*)-yl]-4(3*H*)-quinazolinone dihydrochloride;

5 5-isopropyl-7-methoxy-2-[5-[(pyridin-2-ylmethyl)amino]-3,4-dihydro-2,6-naphthyridin-2(1*H*)-yl]-4(3*H*)-quinazolinone dihydrochloride;

5-isopropyl-7-methoxy-2-[5-[[2-methoxyethyl)amino]methyl]-3,4-dihydroiso-4(3*H*)-quinolin-2(1*H*)-yl]-4(3*H*)-quinazolinone dihydrochloride;

10 2-[5-[[2-(dimethylamino)ethyl]amino]-3,4-dihydro-2,6-naphthyridin-2(1*H*)-yl]-5-isopropyl-7-methoxy-4(3*H*)-quinazolinone trihydrochloride;

2-[5-[(dimethylamino)methyl]-3,4-dihydroiso-4(3*H*)-quinolin-2(1*H*)-yl]-5-isopropyl-7-methoxy-4(3*H*)-quinazolinone dihydrochloride;

2-[4-amino-2-(dimethylamino)-5,8-dihydropyrido[3,4-*d*]pyrimidin-7(6*H*)-yl]-5-isopropyl-7-methoxy-4(3*H*)-quinazolinone dihydrochloride;

15 2-[2-(dimethylamino)-4-[(2-methoxyethyl)amino]-5,8-dihydropyrido[3,4-*d*]pyrimidin-7(6*H*)-yl]-5-isopropyl-7-methoxy-4(3*H*)-quinazolinone trihydrochloride;

5-isopropyl-7-methoxy-2-[5-[(4-methoxypiperidin-1-yl)methyl]-3,4-dihydro-2,6-naphthyridin-2(1*H*)-yl]-4(3*H*)-quinazolinone dihydrochloride;

20 5-isopropyl-7-methoxy-2-[5-[(3-methoxyazetidin-1-yl)methyl]-3,4-dihydro-2,6-naphthyridin-2(1*H*)-yl]-4(3*H*)-quinazolinone dihydrochloride;

5-isopropyl-7-methoxy-2-[2-(morpholin-4-ylmethyl)-7,8-dihydropyrido[4,3-*d*]pyrimidin-6(5*H*)-yl]-4(3*H*)-quinazolinone dihydrochloride;

2-[5-[(dimethylamino)methyl]-3,4-dihydro-2,6-naphthyridin-2(1*H*)-yl]-5-isopropyl-7-methoxy-4(3*H*)-quinazolinone dihydrochloride;

25 2-[2-[[2-(dimethylamino)ethyl]amino]-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl]-5-isopropyl-7-methoxy-4(3*H*)-quinazolinone trihydrochloride;

5-isopropyl-7-methoxy-2-[5-[(2-methyl-1*H*-imidazol-1-yl)methyl]-3,4-dihydroiso-4(3*H*)-quinolin-2(1*H*)-yl]-4(3*H*)-quinazolinone dihydrochloride;

30 7-methoxy-2-[2-[[2-methoxyethyl)(methyl)amino]methyl]-7,8-dihydropyrido[4,3-*d*]pyrimidin-6(5*H*)-yl]-5-tetrahydro-2*H*-pyran-4-yl-4(3*H*)-quinazolinone dihydrochloride;

7-methoxy-2-[2-(pyrrolidin-1-ylmethyl)-7,8-dihydropyrido[4,3-*d*]pyrimidin-6(5*H*)-yl]-5-tetrahydro-2*H*-pyran-4-yl-4(3*H*)-quinazolinone dihydrochloride;

2-(2-[(dimethylamino)methyl]-7,8-dihydropyrido[4,3-*d*]pyrimidin-6(5*H*)-yl)-7-methoxy-5-tetrahydro-2*H*-pyran-4-yl-4(3*H*)-quinazolinone dihydrochloride;

- 7-methoxy-2-[5-(pyrrolidin-1-ylmethyl)-3,4-dihydro-2,6-naphthyridin-2(1H)-yl]-5-tetrahydro-2H-pyran-4-yl-4(3H)-quinazolinone dihydrochloride;
- 2-(5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)-7-methoxy-5-tetrahydro-2H-pyran-4-yl-4(3H)-quinazolinone hydrochloride;
- 5 7-methoxy-2-[5-(morpholin-4-ylmethyl)-3,4-dihydro-2,6-naphthyridin-2(1H)-yl]-5-tetrahydro-2H-pyran-4-yl-4(3H)-quinazolinone dihydrochloride;
- 2-[5-[(dimethylamino)methyl]-3,4-dihydro-2,6-naphthyridin-2(1H)-yl]-7-methoxy-5-tetrahydro-2H-pyran-4-yl-4(3H)-quinazolinone dihydrochloride;
- 7-methoxy-2-[5-(morpholin-4-ylmethyl)-3,4-dihydroiso-4(3H)-quinolin-2(1H)-yl]-5-tetrahydro-2H-pyran-4-yl-4(3H)-quinazolinone dihydrochloride;
- 10 7-methoxy-2-[5-[(3-methoxyazetidin-1-yl)methyl]-3,4-dihydroiso-4(3H)-quinolin-2(1H)-yl]-5-tetrahydro-2H-pyran-4-yl-4(3H)-quinazolinone dihydrochloride;
- 7-methoxy-2-[2-[(2-pyrrolidin-1-ylethyl)amino]-7,8-dihydro-1,6-naphthyridin-6(5H)-yl]-5-tetrahydrofuran-2-yl-4(3H)-quinazolinone trihydrochloride;
- 15 7-methoxy-2-[2-[(2-methoxyethyl)amino]-7,8-dihydro-1,6-naphthyridin-6(5H)-yl]-5-tetrahydrofuran-2-yl-4(3H)-quinazolinone dihydrochloride;
- 2-[2-[(2-(dimethylamino)ethyl)amino]-7,8-dihydro-1,6-naphthyridin-6(5H)-yl]-7-methoxy-5-tetrahydrofuran-2-yl-4(3H)-quinazolinone trihydrochloride;
- 2-(5-amino-3,4-dihydro-2,6-naphthyridin-2(1H)-yl)-7-methoxy-5-tetrahydrofuran-2-yl-4(3H)-quinazolinone trihydrochloride;
- 20 5-chloro-7-methoxy-2-[2-(pyrrolidin-1-ylmethyl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl]-4(3H)-quinazolinone dihydrochloride;
- 5-chloro-7-methoxy-2-(5-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone dihydrochloride;
- 25 5-cyclopropyl-2-[2-[(ethyl(2-methoxyethyl)amino)methyl]-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl]-7-methoxy-4(3H)-quinazolinone dihydrochloride;
- 2-[2-(aminomethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl]-5-isopropyl-7-methoxy-4(3H)-quinazolinone dihydrochloride;
- 2-(7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-7-methoxy-5-(1-methylpiperidin-2-yl)-4(3H)-quinazolinone trihydrochloride;
- 30 2-(6,7-dimethoxy-3,4-dihydroiso-4(3H)-quinolin-2(1H)-yl)-7-methoxy-5-(1-methylpiperidin-2-yl)-4(3H)-quinazolinone dihydrochloride;
- 7-methoxy-2-[2-[(2-methoxyethyl)amino]-7,8-dihydro-1,6-naphthyridin-6(5H)-yl]-5-(1-methylpiperidin-2-yl)-4(3H)-quinazolinone trihydrochloride;

5-(butylsulfonyl)-7-methoxy-2-[5-[(2-methoxyethyl)amino]-3,4-dihydro-2,6-naphthyridin-2(1*H*)-yl]-4(3*H*)-quinazolinone;

5-(butylsulfonyl)-7-methoxy-2-[5-[(pyridin-2-ylmethyl)amino]-3,4-dihydro-2,6-naphthyridin-2(1*H*)-yl]-4(3*H*)-quinazolinone;

5 5-isopropyl-7-methoxy-2-[1-(2-pyrrolidin-1-ylethyl)-1,4,6,7-tetrahydro-5*H*-pyrazolo[4,3-*c*]pyridin-5-yl]-4(3*H*)-quinazolinone;

5-isopropyl-7-methoxy-2-[2-(2-pyrrolidin-1-ylethyl)-2,4,6,7-tetrahydro-5*H*-pyrazolo[4,3-*c*]pyridin-5-yl]-4(3*H*)-quinazolinone;

5-chloro-7-methoxy-2-[5-(pyrrolidin-1-ylmethyl)-3,4-dihydro-2,6-naphthyridin-10 2(1*H*)-yl]-4(3*H*)-quinazolinone;

5-isopropyl-7-methoxy-2-[2-(4-methylpiperazin-1-yl)-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl]-4(3*H*)-quinazolinone trihydrochloride;

5-Isopropyl-7-methoxy-2-(5-methylaminomethyl-3,4-dihydro-1*H*-[2,6]naphthyridin-2-yl)-3*H*-quinazolin-4-one dihydrochloride;

15 and pharmaceutically acceptable salts or solvates thereof.

The compounds of the invention are useful because they possess pharmacological activity in animals. In particular, the compounds are useful in the treatment of a number of conditions including hypertension, myocardial infarction, male erectile dysfunction, 20 hyperlipidaemia, cardiac arrhythmia, glaucoma and benign prostatic hyperplasia. They may also be useful in the treatment of female sexual arousal dysfunction. Benign prostatic hyperplasia is of greatest interest.

Thus, according to another aspect of the invention, there is provided a pharmaceutical 25 composition including a compound of the formula (I), a tautomer, or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipient, diluent or carrier. Also provided is a method of treatment of benign prostatic hyperplasia, which comprises administering a therapeutically effective amount of a compound of the invention to a patient suffering from such a disorder. The use of the 30 compounds of the invention as pharmaceuticals, and the use of the compounds of the invention in the manufacture of a medicament for the treatment of benign prostatic hyperplasia, are also provided.

The compounds of the invention may be administered by any convenient route, for 35 example orally, parenterally (e.g. intravenously, transdermally) or rectally. The daily dose

required will of course vary with the particular compound used, the particular condition being treated and with the severity of that condition. However, in general a total daily dose of from about 0.01 to 10.0 mg/kg of body weight, and preferably about 0.01 to 2.5 mg/kg, is suitable, administered from 1 to 2 times a day. Oral administration is of particular interest.

The compounds of the invention will generally be administered in the form of a suitable pharmaceutical formulation. Thus, according to another aspect of the invention, there is provided a pharmaceutical formulation including preferably less than 50% by weight of a compound of the invention in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier. The pharmaceutical formulation is preferably in unit dose form. Such forms include solid dosage forms, for example tablets, pills, capsules, powders, granules, and suppositories for oral, parenteral or rectal administration; and liquid dosage forms, for example sterile parenteral solutions or suspensions, suitably flavoured syrups, flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil and peanut oil, and elixirs and similar pharmaceutical vehicles. Oral formulations are preferably controlled-release formulations.

Solid formulations may be prepared by mixing the active ingredient with pharmaceutical carriers, for example conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate, gums and other diluents, for example water, to form a homogeneous preformulation formulation in which the active ingredient is uniformly dispersed so that it may be readily subdivided into equally effective unit dosage forms containing typically from 1.0 to about 70.0 mg of the active ingredient. The solid dosage forms may be coated or otherwise compounded to prolong the action of the formulation.

Formulations intended for the treatment of benign prostatic hyperplasia may contain a compound of the invention in combination with a compound that attenuates the growth of the prostate gland. For example, a formulation is envisaged that combines a compound of the invention with human 5- α reductase inhibitory compound [see International Patent Application WO 95/28397]. Alternatively, a compound of the invention could be presented in a pharmaceutical pack also containing a human 5- α reductase inhibitory compound as a combined preparation for simultaneous, separate or sequential use.

The compounds of the invention may be tested in the screen set out below:

Contractile responses of rabbit aorta (α_{1L} receptor)

A single rabbit aorta was cleaned of connective tissue, cut into rings ~3mm in length, then denuded of epithelium by rubbing very gently with a probe. The lengths of tissue are then mounted in the 5mL organ baths, which contain the modified Krebs of the following composition (mM): NaCl (119), KCl (4.7), CaCl_2 (2.5), KH_2PO_4 (1.2), MgSO_4 (1.2), NaHCO_3 (25), glucose (11), and gassed with 95% O_2 /5% CO_2 . The tissues are placed under ~1.5g tension, and are left to equilibrate for ~60 minutes on a pump speed of ~5mL/minute, adjusting the tension to 1-1.5g if necessary after 15 and 45 minutes. A 1M stock solution ($1 \times 10^{-3}\text{M}$ bath conc.) of methoxamine in water was made and 1:10 dilutions made using the same diluent. A sensitising dose of 120mM KCl (bath concentration) was added to each bath. After the maximum response had been reached (usually about 6-8 minutes), the tissues are washed with Krebs solution for 60 minutes, pump speed at ~2.97mL/min.

A cumulative dose response curve was constructed, bath concentrations of methoxamine being $1 \times 10^{-7}\text{M}$ to a maximum of $3 \times 10^{-4}\text{M}$. Each dose was allowed to exert its maximum effect before the next dose was added (6-8 mins). On completion of this curve, the tissues were washed, (pump speed ~10mL/min for 10 minutes, 2.97mL/min for 50 minutes) until the tissues were stable at baseline tension.

The compound under investigation was made up to a stock concentration of 1mM in 100% DMSO. Three chosen concentrations for a pA_2 estimation were then made up in DMSO, and 5 μL of each concentration added in duplicate to the tissues, with a vehicle control (DMSO). The tissues were left in the presence of compound or vehicle for 60 minutes before a second CDRC to methoxamine was constructed up to a maximum of $3 \times 10^{-3}\text{M}$.

The data was captured on ADA analysis in-vitro software, which expresses the readings as a % of the maximum response of the control curve, draws control and test compound dose response curves, and calculates a EC_{50} and then dose ratio (DR), the ratio between control and treatment curve EC_{50} , for each treatment. The results are reported as pK_b , or where possible pA_2 .

$$pK_b = \frac{-\log [\text{Antagonist concentration}]}{(DR^* - 1)}$$

where $DR^* = \frac{\text{dose ratio compound}}{\text{dose ratio control}}$

5

NB. If the value of (DR^*-1) was less than or equal to 2, the result could not be used for a pA_2 estimation. The control curves must not have shifted by more than 2.5. The pA_2 was plotted on a Schild analysis. i.e. y axis = $\log (DR^*-1)$; x axis = $-\log$ antagonist concentration

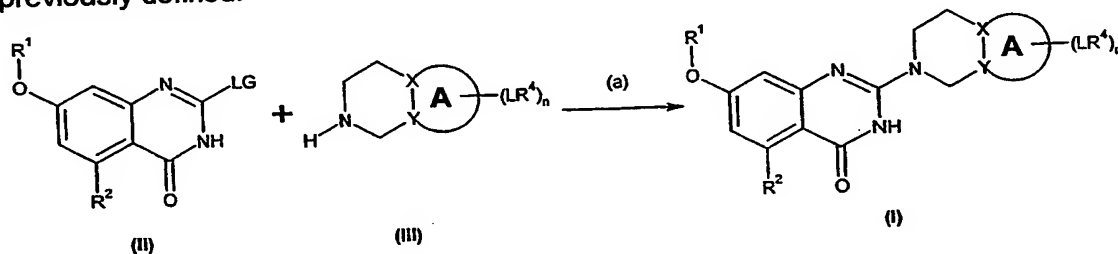
10

The compounds of the invention may have the advantage that they are more potent, have a longer duration of action, have a broader range of activity, are more stable, have fewer side effects or are more selective (in particular they may have beneficial effects in benign prostatic hyperplasia without causing undesirable cardiovascular effects, for example because they are able to selectively antagonise prostatic receptor subtypes of the α_1 -adrenoceptor), or have other more useful properties than the compounds of the prior art. It will be apparent to those skilled in the art that sensitive functional groups may need to be protected and deprotected during synthesis of a compound of the invention. This may be achieved by conventional techniques, for example as described in 'Protective Groups in Organic Synthesis' by T W Greene and P G M Wuts, John Wiley and Sons Inc, 1991.

20

The compounds of the invention may be obtained by the reaction of an amine (III) with alkylating agent (II) as shown in the scheme below, where R^1 , R^2 , X, Y etc. are as previously defined:

25



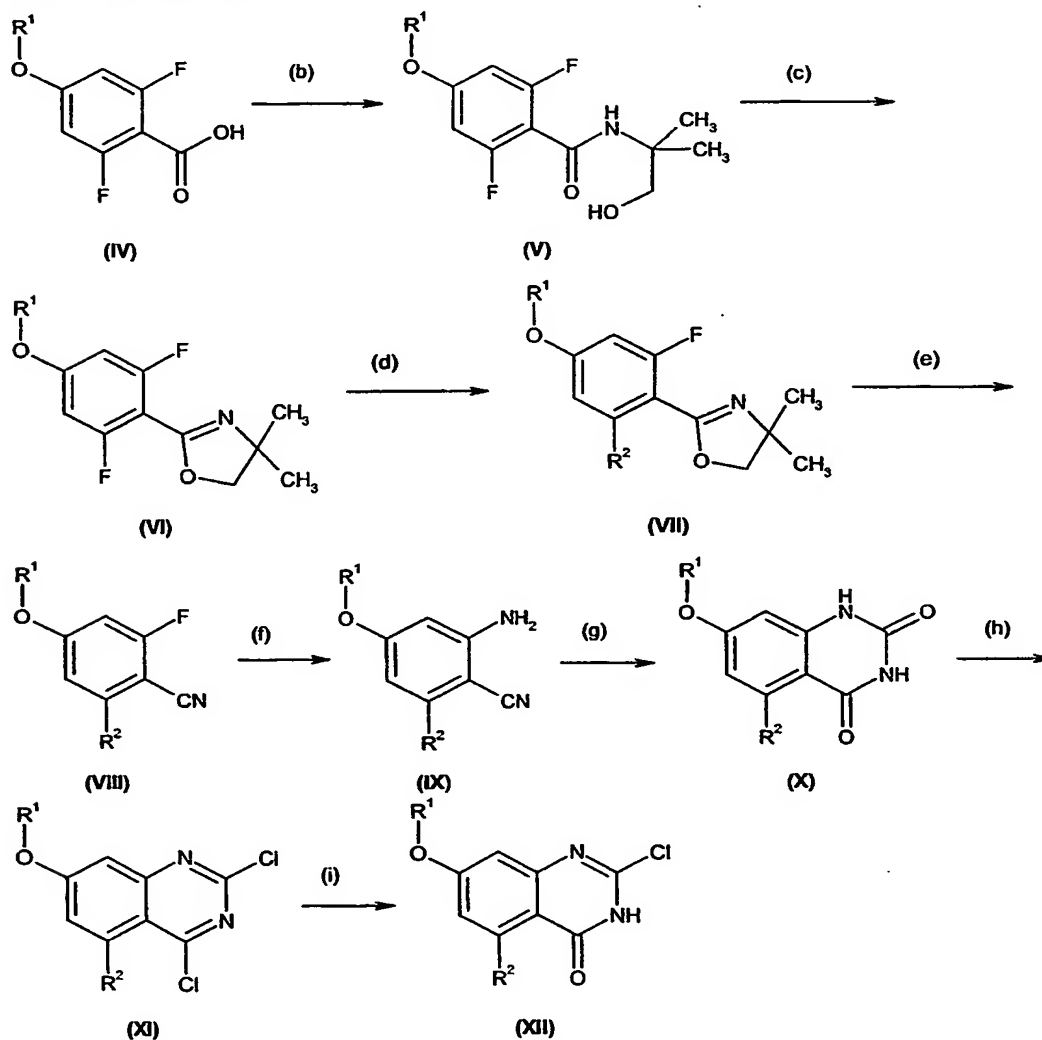
Scheme 1.

Step (a): Amine (III) is reacted with quinazolinone (II), where LG is a suitable leaving group (for example halo, tosylate or mesylate), in the presence of an excess of 3° amine base (as H^+ acceptor) (for example Et_3N , Hünig's base or NMM) in a suitable high boiling solvent at elevated temperature for 1-6 hrs. For example, preferred

30

conditions for a) are 1-2 eq. amine (III), 1.5-8 eq. of 3° amine base (for example Et₃N or Hünig's base), in n-BuOH at reflux for 1-6 hours. Preferably leaving group LG is Halo. More preferably LG is Cl.

- 5 Quinazolinone (II) may be prepared according to scheme 2, where R¹ and R² are as previously defined:



Scheme 2.

Step (b): This acid/amine coupling may be undertaken by using either

- 15 (i) an acyl chloride derivative of acid (IV) + amine, with an excess of acid acceptor in a suitable solvent, or

(ii) the acid (IV) with a conventional coupling agent + amine, optionally in the presence of a catalyst, with an excess of acid acceptor in a suitable solvent.

Typically the conditions are as follows:

5 acid chloride of acid (IV) (generated in-situ), an excess of amine, optionally with an excess of 3° amine such as Et₃N, Hünig's base or NMM, in DCM or THF, without heating for 1 to 24 hrs,

or

10 (ii) acid (IV), WSCDI /DCC and HOBT /HOAT, an excess of amine, with an excess of NMM, Et₃N, Hünig's base in THF, DCM or EtOAc, at rt. for 4 to 48 hrs; or, acid (IV), PYBOP®/PyBrOP®/Mukaiyama's reagent, an excess of amine, with an excess of NMM, Et₃N, Hünig's base in THF, DCM or EtOAc, at rt. for 4 to 24 hrs.

15 The preferred conditions are: acid chloride of acid (IV) (generated in-situ), 3.6 eq. amine, in DCM at r.t. for 1hr.

Step (c): The hydroxy group of compound (V) is converted into a suitable leaving group (LG, where LG is halo, mesylate, or tosylate), followed by an in-situ alkylation/ring formation.

20

Typically LG is halo. It is preferred that LG is Cl. Chlorination is carried out under standard conditions, using a chlorinating agent (SOCl₂, POCl₃) optionally in the presence of a 3° amine base (e.g. Hünig's base, Et₃N), optionally in a suitable solvent (DCM) at room temperature to reflux temperature for 1-16 hours. Preferred conditions

25 are: 1.1 eq. SOCl₂, in DCM for 1.5 hrs at rt.

Step (d): An organometallic addition/elimination is undertaken by reacting fluoro compound (VI) with "activated" R² (such as R²MgBr, R²MgCl, R²Li), in a suitable solvent (tetrahydrofuran, ether, cyclohexane, 1,4-dioxane) at 0°C to room temperature

30 for 1-24 hrs. Preferred conditions are: 1-2 eq. of R²MgBr or R²MgCl (generated in-situ, using standard Grignard methodology), 1 eq. of fluoro compound (VI), in tetrahydrofuran, at between 0°C and room temperature, for 3 hours.

Step (e): The nitrile (VIII) is preferably formed from compound (VII) under the following conditions: 2 eq. POCl₃, 10 eq. pyridine, EtOAc, reflux for 5 hours.

35

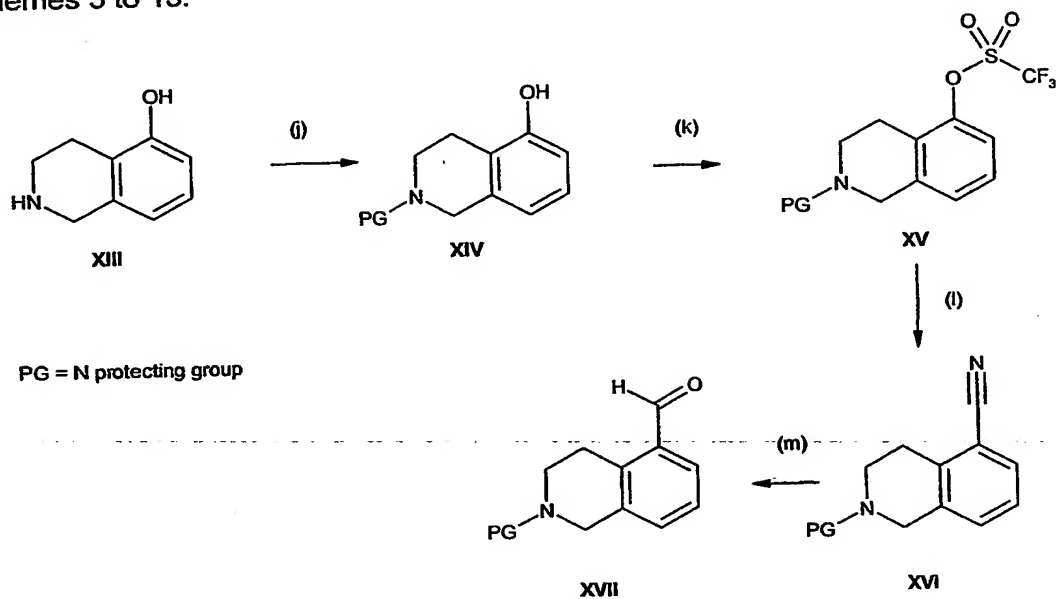
Step (f): Amination of compound (VIII) is achieved by reaction with R^aNH_2 (R^a is H) at an elevated temperature and pressure, in a suitable solvent (DMSO, MeOH) for about 18-72 hrs. It is preferred to carry out the reaction under the following conditions: R^aNH_2 in DMSO at elevated temperature (about 140°C) and pressure (sealed vessel) for 18-
5 72 hrs.

Step (g): Quinazolinedione (X) is formed by CO_2 insertion, derived from the method of Mizuno et. al. Tet. Lett. 41 (2000) 1051. The following conditions are preferred: 2 eq. of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), CO_2 (solid), in N,N-dimethylformamide, at
10 140°C and elevated pressure (sealed vessel) for 18 hrs.

Step (h): This chlorination step can be done under standard conditions, using an excess of chlorinating agent ($SOCl_2$, $POCl_3$) optionally in the presence of a 3° amine base (e.g. Hünig's base, Et_3N), optionally in a suitable solvent (DCM) at room
15 temperature to reflux temperature for 1-16 hours. It is preferred to use the following conditions: 30 eq. $POCl_3$ (as solvent), optionally in the presence of a base, e.g. 2.4 eq. Hünig's base, at reflux for 1-7 hours

Step (i): Selective hydrolysis of compound (XI) is achieved by reaction with an OH^- source (typically an alkali metal hydroxide) in a suitable solvent, at room temperature
20 for 2 hours. Preferred conditions are: 3 eq. $NaOH(aq.)$ in dioxane at room temperature for 2 hours.

Suitable amines for use as compound (III) may be prepared as described below in schemes 3 to 13:

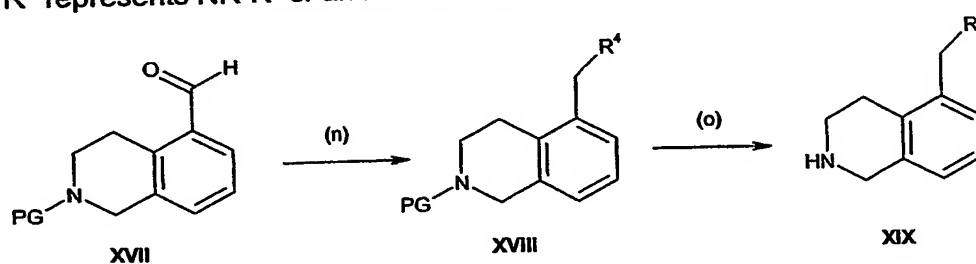


Scheme 3.

5

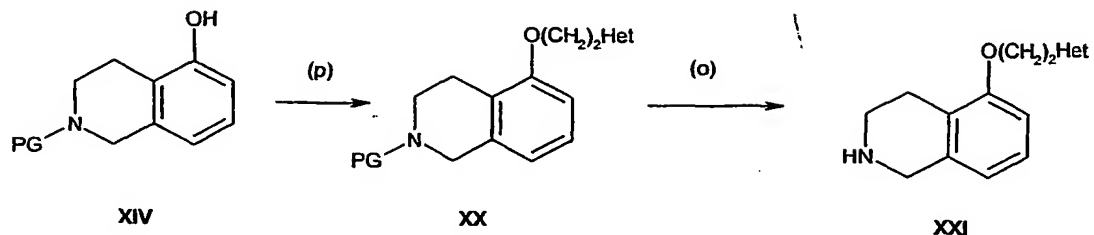
Compounds XVII and XIV can then be further elaborated according to schemes 4 and 5 respectively:

when R^4 represents NR^5R^6 or an N-linked Het,



10

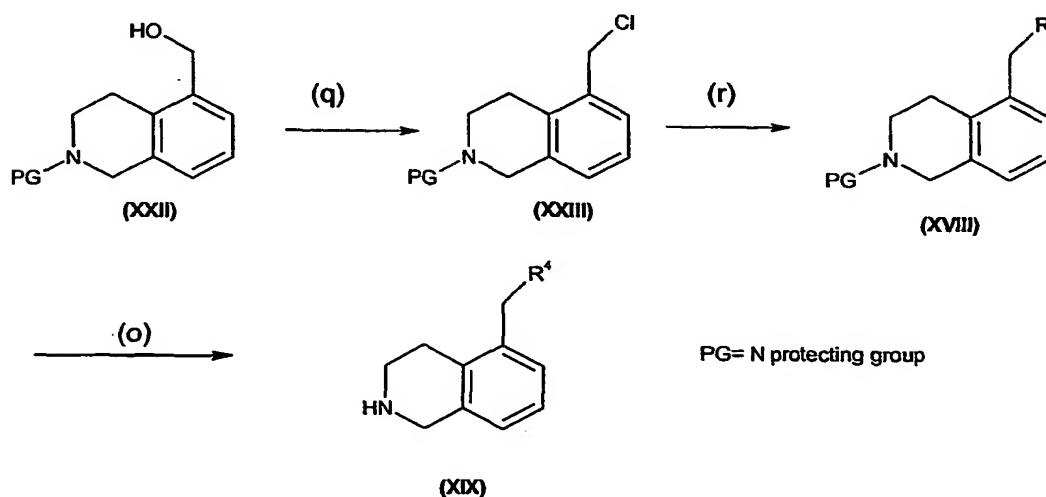
Scheme 4.



PG = N protecting group

Scheme 5.

When R^4 represents NR^5R^6 or N-linked Het, compounds of formula (XIX) may also be prepared according to scheme 6:



PG = N protecting group

Scheme 6

Step (j): The amine (XIII) is protected using standard methodology for introducing nitrogen protecting groups, such as that found in textbooks, (e.g. "Protecting Groups in Organic Synthesis" by T.W. Greene and P. Wutz). It is preferred to use the *tert*-butoxycarbonyl (Boc) protecting group which is introduced under the following conditions: 2.3 eq. $(Boc)_2O$, in dioxane/1N NaOH solution (1:2 by volume) at room temperature for 16 hrs.

Step (k): Triflate (XV) is formed by reaction of alcohol (XIV) with a slight excess of a suitable triflating reagent, in the presence of an excess of a 3° amine base (e.g. Et_3N , NMM, Hünig's base) in a suitable solvent (DCM) at between $-30^\circ C$ and room temperature for up to 24 hours. Preferred conditions are as follows: 1.1 eq. N-phenylbis(trifluoromethanesulphonimide) or triflic anhydride, 1.1 eq. Et_3N , in DCM at $0^\circ C$ and room temperature for 2 to 16 hours.

Step (l): Nitrile (XVI) is obtained via metal catalysed (preferably palladium, nickel) cross-coupling with a suitable nitrile source (e.g. $\text{Zn}(\text{CN})_2$), in the presence of a suitable additive (preferably LiCl) in a suitable solvent at elevated temperature for up to 24 hrs. It is preferred to use the following conditions: 1 eq. $\text{Zn}(\text{CN})_2$, 1 eq. LiCl, cat $\text{Pd}(\text{PPh}_3)_4$,
5 in N,N-dimethylformamide at 110-125°C for 8 to 24 hrs.

Step (m): Nitrile (XVI) is reduced with a suitable metal hydride reducing agent (LiAlH_4 , NaAlH_4 , DIBAL-H) in a suitable solvent (toluene, tetrahydrofuran) at low temp (-78°C), followed by acid or base catalysed hydrolysis of the intermediate imine compound to
10 give aldehyde (XVII). Preferred conditions are: 2 eq. DIBAL-H, in toluene at -78°C for 2 hrs, then MeOH, HCl at -78°C to 0°C.

Step (n): Aldehyde (XVII) is reacted with an amine (NR^5R^6 or N-linked Het) to form an intermediate compound, which is reduced by a suitable reducing agent, such as
15 $\text{NaCN}(\text{BH})_3$ or $\text{Na}(\text{OAc})_3\text{BH}$, optionally in the presence of NaOAc or AcOH, optionally in the presence of a drying agent (molecular sieves, MgSO_4) in a suitable solvent (tetrahydrofuran, DCM) at room temperature for 3-72 hrs. Preferred conditions are: 1-2 eq. amine, 2-5 eq. of $\text{Na}(\text{OAc})_3\text{BH}$, optionally with 1-4 eq. of AcOH or NaOAc, optionally in the presence of 3Å sieves, in tetrahydrofuran at room temperature for 3-72
20 hrs.

Step (o): Deprotection is undertaken using standard methodology, as described in "Protecting Groups in Organic Synthesis" by T.W. Greene and P. Wutz".
25 When PG is Boc, then preferred conditions are: HCl(g) in DCM or MeOH at rt. for 30 min to 2 hrs, or DCM:TFA (1:1 by volume) at room temperature for 3 hrs.

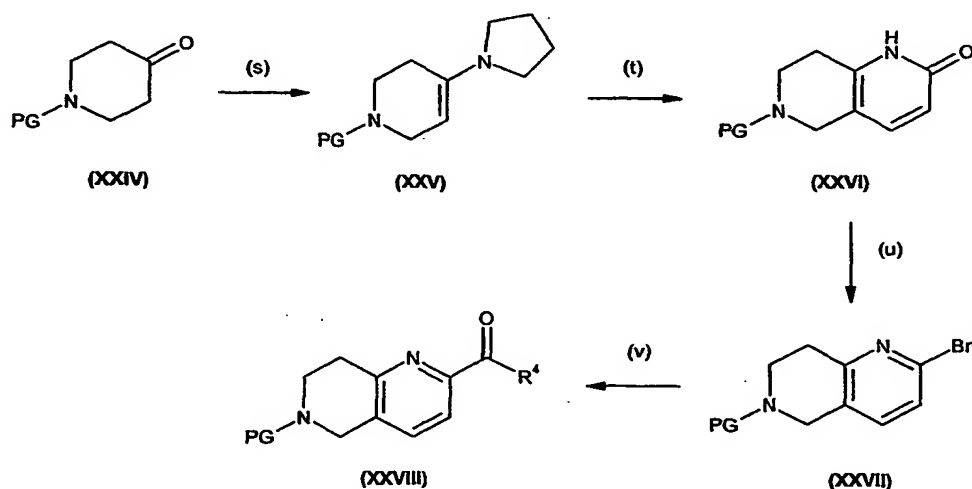
When PG is benzyl, then the preferred conditions are: 10% Pd/C (1:1 w/w), 2-25 eq. ammonium formate or formic acid, in MeOH at reflux for between 3 mins and 1.5 hrs,
30 or 10% Pd/C (about 10% w/w), in methanol, optionally in the presence of HCl, at about 30°C and 30psi for about 17 hrs.

Step (p): A Mitsunobu reaction between alcohol (XIV) and $\text{HO}(\text{CH}_2)_2\text{Het}$ is carried out using standard methodology, as discussed in Synthesis 1 (1981) or Org. React. 42;

335 (1992). Preferred conditions are: 2.1 eq. DEAD (Diethylazodicarboxylate), 2.25 eq. PPh_3 , 2.65 eq. of $\text{HO}(\text{CH}_2)_2\text{Het}$, in DCM for 34 hrs at rt.

5 **Step q:** The alcohol (XXII) (when Prot is Boc, the alcohol may be obtained as described in WO 02/053558) may be chlorinated to provide the chloride (XXIII) using standard methodology, but preferably under non-acidic conditions. Preferred conditions are: 1.2 eq. MeSO_2Cl , and 1.5 eq. Et_3N , in tetrahydrofuran for 30 mins, followed by 1.5 eq. Bu_4NCl , at r.t. for about 2 hours.

10 **Step (r):** The chloride (XXIII) is reacted with an amine ($\text{R}^5\text{R}^6\text{NH}$) or N-linked Het, in the presence of a suitable base (e.g. alkali metal hydride, such as NaH or LiH) in a suitable solvent (e.g. ether, tetrahydrofuran) at between room temperature and reflux for up to 18 hours to provide compounds of formula (XVIII). Preferred conditions are: 1.05eq. NaH, 1.1 eq. amine/N-linked Het, in tetrahydrofuran at between r.t. and reflux for 18
15 hrs.



Scheme 7.

20 **Step (s):** Compound (XXIV) is reacted with pyrrolidine, with the concomitant removal of water, in a suitable high boiling solvent, at an elevated temperature for up to 48 hours, to give compound (XXV). The following conditions are preferred: 1.5 eq. pyrrolidine and ketone (XXII) in toluene at reflux under Dean and Stark conditions, for 4.5 hrs.

25 **Step (t):** 2 equivalents of propiolamide to 1 equivalent of compound (XXV) in a high boiling solvent (e.g. Toluene) at reflux for 16 hours.

Step (u): Compound (XXVI) is brominated using standard methodology, with a suitable brominating agent (POBr_3), optionally in the presence of anisole, in a suitable solvent (MeCN), at elevated temp for about 1 hr. The following conditions are preferred: 5 eq. of POBr_3 , in MeCN/anisole (1:1 by volume) at 120°C for 1 hr.

5

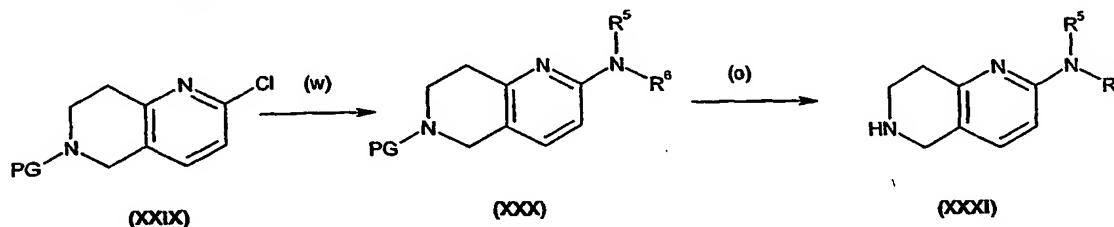
Step (v): Metalation of compound (XXVII) is undertaken with a suitable base ($n\text{BuLi}$) at low temp (-78°C), followed by quench of the intermediate anion by an excess of carbonyl or formyl source (N,N-dimethylformamide) for about 1 hr, to give the desired compound. Preferred conditions are: 1.1-1.5 eq. $n\text{-BuLi}$, tetrahydrofuran, -78°C , for 5-15min, then 3eq N,N-dimethylformamide or R^4COH for 1 hour.

10

Compound (XXVIII), when R^4 in scheme 7 represents H, can then be further elaborated by reductive amination followed by deprotection in a manner similar to that depicted in scheme 4.

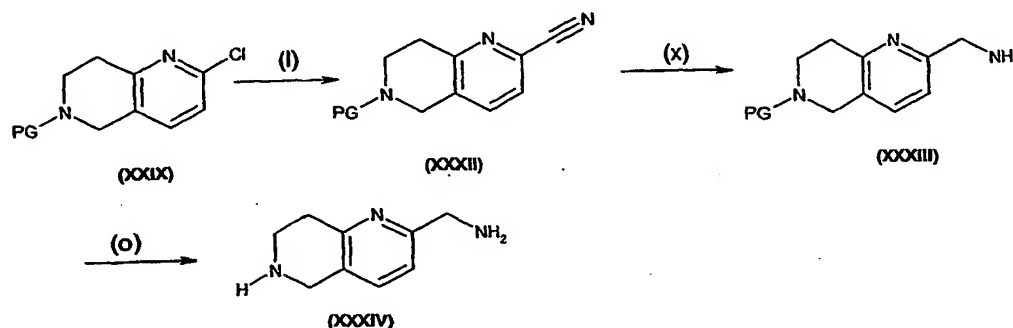
15

Compounds (XXIX) and (XXVII) can be further elaborated according to schemes 8, 9, 10, and 11 respectively. PG represents a N-protecting group, preferably Bn:

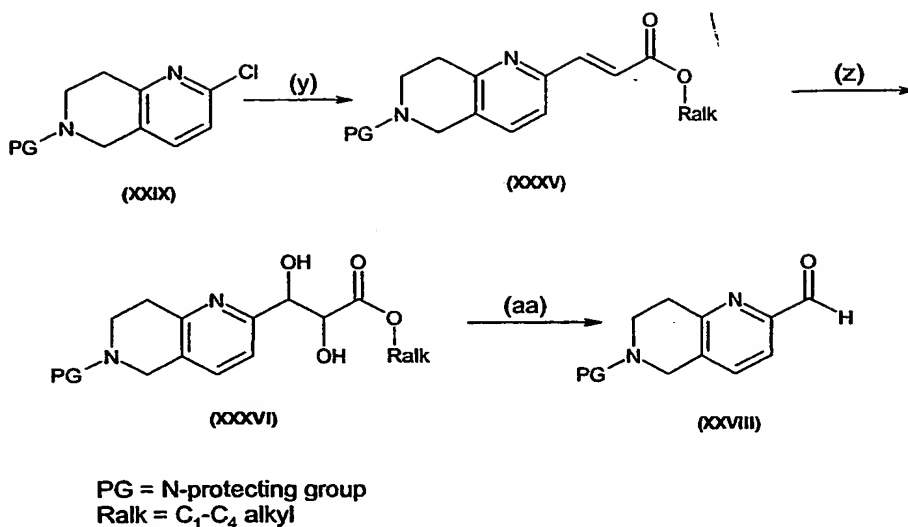


Scheme 8.

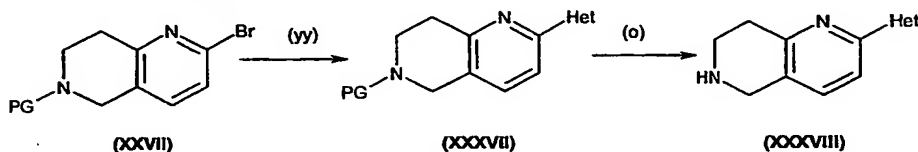
20



Scheme 9

**Scheme 10.**

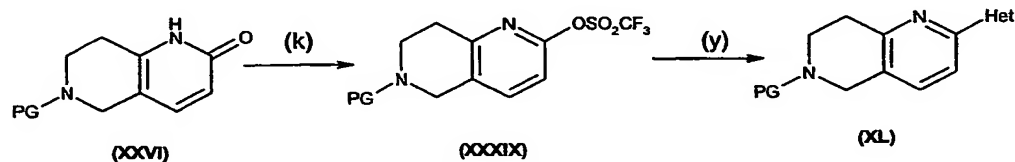
When Het is linked through N,



5

Scheme 11.

Compound (XXVI) may be further reacted to provide compounds where Het is linked through C, according to scheme 12:



10

Scheme 12.

Step (w): Amination of compound (XXIX) (when PG is Bn, obtained as described in WO 9830560) is achieved by reaction with R⁵R⁶NH at elevated temperature and pressure, optionally in a suitable solvent (DMSO, MeOH) and optionally in the presence of a suitable catalyst, for about 18-72 hrs. It is preferred to carry out the reaction under the following conditions: R⁵R⁶NH optionally in DMSO at the reflux temperature of the reaction, at elevated pressure (sealed vessel) for 18-72 hrs, optionally in the presence of CuSO₄.

15

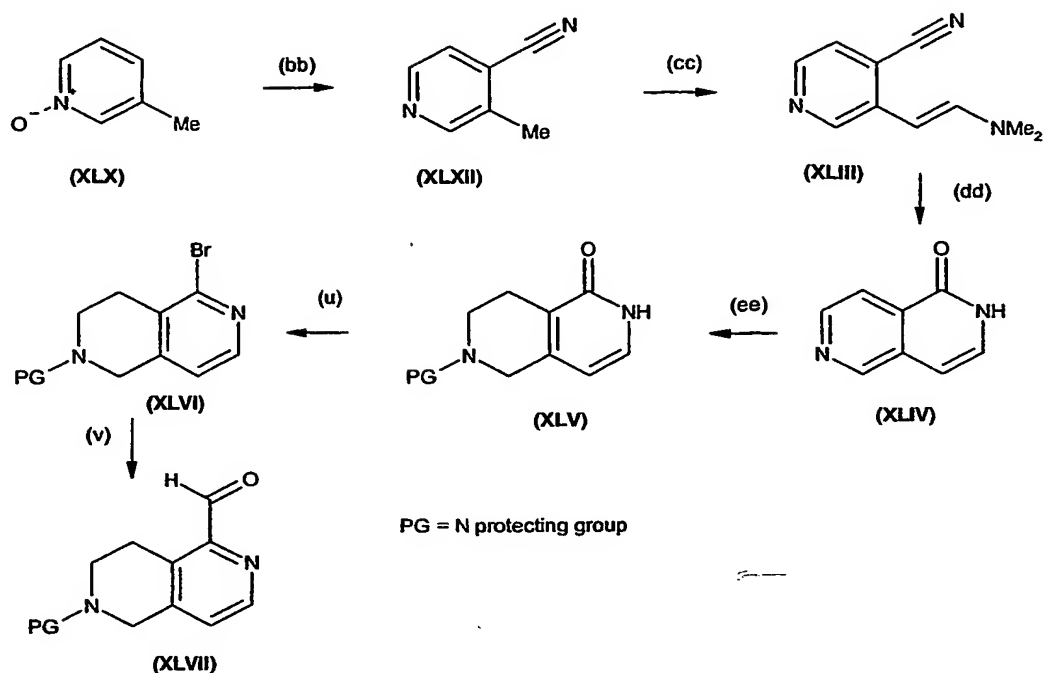
Step (x): Reduction of the nitrile (XXXII) to provide the amine (XXXIII) may be achieved using a suitable reducing agent (LiAlH_4 , $\text{BH}_3\text{Me}_2\text{S}$) or by hydrogenation in the presence of a suitable metal (e.g. Raney® Nickel). Typically the reaction is carried out according to the method of Satoh and Suzuki (Tet. Lett. 4555; 1969). The preferred conditions are: 2 eq. CoCl_2 , 10 eq. NaBH_4 in MeOH at r.t. for up to 2 hrs.

Step (y): A metal (e.g. palladium, nickel or zinc) catalysed cross-coupling reaction is undertaken, optionally using a suitable base ($\text{Na}^t\text{-BuO}$, K_2CO_3 or Et_3N), a catalytic amount of suitable additive and metal catalyst in a suitable solvent such as toluene, dioxan or N,N-dimethylformamide at elevated temp for up to 18 hrs, to give the desired compound. The preferred conditions are: 3 eq. vinyl ester, 0.1 eq. $\text{Pd}(\text{dba})_3$, 0.3 eq. $\text{P}(\text{t-Bu})_3$, excess Et_3N in dioxan at reflux for 17 hrs.

Step (yy): A metal (e.g. palladium, nickel or zinc) catalysed cross-coupling reaction is undertaken, optionally using a suitable base ($\text{Na}^t\text{-BuO}$, K_2CO_3 or Et_3N), a catalytic amount of suitable additive and metal catalyst in a suitable solvent such as toluene, dioxan or N,N-dimethylformamide at elevated temp for up to 18 hrs, to give the desired compound. The preferred conditions are: 1.5 eq. Het, (e.g. morpholine), 1.5 eq. $\text{Na}^t\text{-BuO}$, 0.08eq BINAP, 0.04 eq. $\text{Pd}(\text{dba})_3$, in toluene at 100°C for 18 hrs.

Step (z) : Hydroxylation of compound (XXXV) using a suitable agent, such as OsO_4 or KMnO_4 optionally in the presence of a suitable oxidant (e.g. NMMO) provides the diol (XXXVI). The preferred conditions are: cat OsO_4 , 1.1 eq. NMMO in H_2O :acetone (1:2 by volume) at r.t. for 72hrs.

Step (aa): The aldehyde (XXVIII) may be obtained from the diol (XXXVI) by oxidation, according to the methods described in Synthesis, 229 (1974). The preferred conditions are: 1.1 eq. NaIO_4 , in MeCN at r.t. for 2 hrs.



Scheme 13.

Step (bb): O-alkylation and addition by cyanide is undertaken using the preferred conditions of 3 eq. EtI, in DCM at rt. for 16 hrs, followed by 2 eq. NaCN in H₂O at 60°C for 1 hr.

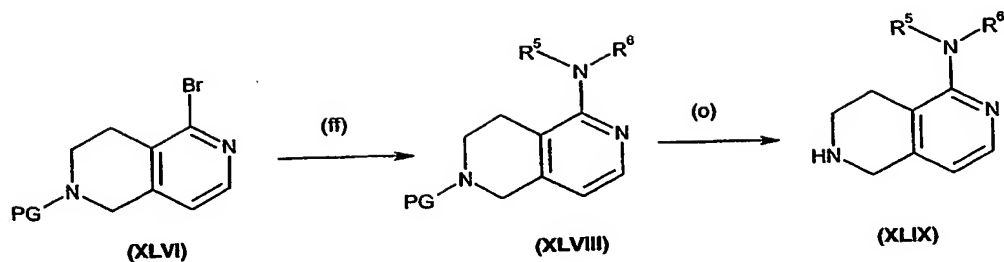
Step (cc): Condensation with N,N-dimethylformamide dimethylacetal is undertaken using the preferred conditions: Substrate (XLXII) in N,N-dimethylformamide/N,N-dimethylformamide dimethylacetal (1:1 to 1:10 by volume) as solvent, at reflux for 8-16 hrs.

Step (dd): Cyclisation is undertaken using the preferred conditions: substrate (XLIII) in EtOH/48% HBr (about 1:1 by volume) for 18 hour.

Step (ee): Protection of the N atom of (XLIV) followed by reduction is achieved using standard methodology, e.g. PG is Benzyl, followed by reduction of the ring using a suitable reducing agent (e.g. NaBH₄). Preferred conditions are 1.5eq benzyl bromide, in MeCN at reflux for 2 hours, followed by an excess of NaBH₄ in EtOH at 0°C to rt. for 16 hrs.

Compound (XLVII) may be further elaborated in a manner analogous to that shown in scheme 4.

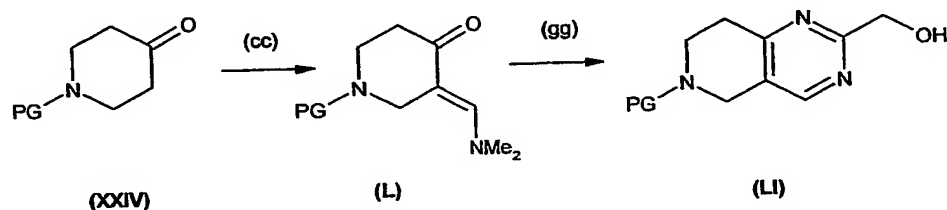
27



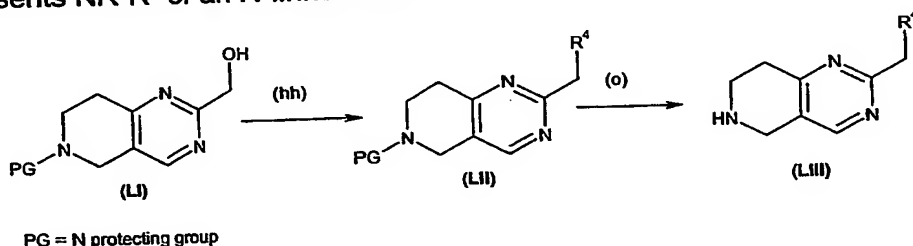
PG = N protecting group

Scheme 14.

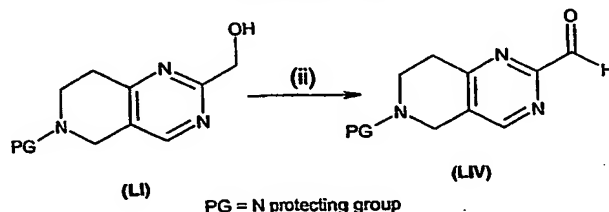
- Step (ff):** Excess amine (R^5R^6NH) is reacted with the bromide (XLVI), optionally in the presence of a 3° amine base (e.g. Hünig's base), at elevated temperature and optionally at elevated pressure, for up to 24 hrs leading to formation of compound (XLVIII). Preferably an excess of amine R^5R^6NH (as solvent) is used, at between 140 and 170°C for up to 20 hrs and optionally at elevated pressure.

**Scheme 15.**

- Compound (LI) can then be elaborated according to scheme 16 and 17 below. When R^4 represents NR^5R^6 or an N-linked Het:



PG = N protecting group

Scheme 16.

PG = N protecting group

Scheme 17.

15

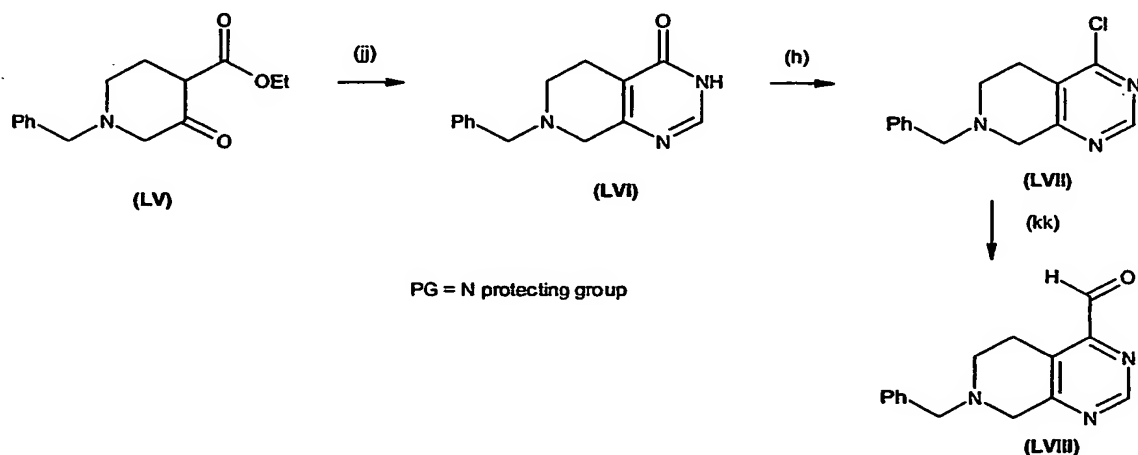
- Step (gg):** Condensation of compound (L) is achieved with a suitable formamidine in the presence of a suitable base (alkali metal alkoxide, or hydride, such as NaOEt, NaH) in a suitable solvent (e.g. EtOH) at elevated temperature. Preferred conditions are:

NaOEt, (generated in-situ), carbonyl compound (L), slight excess of (NH₂CH(N)CH₂OH), in EtOH at reflux for 3 hours.

Step (hh): Alcohol (LI) is reacted, in-situ, to form a suitable alkylating agent (halo, mesylate, tosylate), followed by reaction with an excess of NR⁵R⁶ or an N-linked Het, in the presence of a 3° amine base (Et₃N, Hünig's base) in a suitable solvent. The preferred conditions are: 1.2 eq. MsCl, 2.5 eq-5 eq. NR⁵R⁶ or an N-linked Het, 1.5-2.2 eq. base (Et₃N, Hünig's base) in DCM or tetrahydrofuran for 1-18 hrs between r.t. and reflux.

Step (ii): The aldehyde (LIV) may be obtained by the oxidation of the alcohol (LI) according to the method of Swern, (J.Org. Chem. 41, 957, 1976). The preferred conditions are: 2 eq. DMSO, 1.1 eq. TFAA, in DCM at -60°C for 30 mins, followed by 5 eq. Et₃N.

Compounds of formula (LIV) may be further elaborated using methods analogous to those shown in scheme 4, to provide compounds of formula (LVII).



Scheme 18.

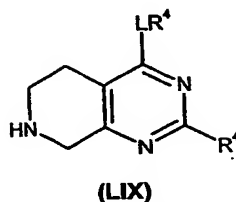
Step (ij): Condensation of the compound (LV) is undertaken with a suitable formamidine in the presence of a suitable base (alkali metal alkoxide, or hydride, such as NaOEt, NaH) in a suitable solvent (e.g. alcohol, EtOH) at elevated temperature. The preferred conditions are: 2.3 eq. NaOEt (generated in-situ), dicarbonyl compound (LV), 1.1eq. formamidine acetate in EtOH at reflux for 40 hrs.

Step (kk)-Metalation of compound (LVII) is undertaken following the method of Kondo et. al (J. Chem. Soc., Perkin Trans. 1, 1996), followed by quench of the intermediate anion by an excess of formyl source (e.g. N,N-dimethylformamide), to provide compound (LVIII). Preferred conditions are: 1.1eq Te, 1.12 eq. n-BuLi, tetrahydrofuran at r.t. for 30 mins, then 1.12eq n-BuLi, excess N,N-dimethylformamide at -78°C for 45 mins.

Compounds (LVIII) may then be elaborated further in an analogous manner to scheme 4.

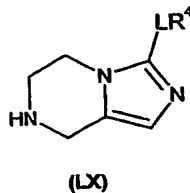
10

Compounds of formula:



may be prepared by analogy to the methods described in WO 02/053558, from readily available starting materials using appropriate reagents and conditions.

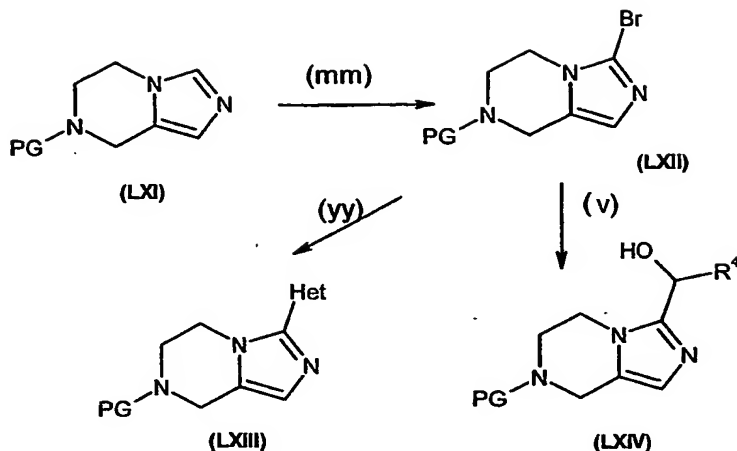
15



Compounds of formula (LX) may be prepared by analogy to the methods described in JP 07101959, and to those described herein, from readily available starting materials using appropriate reagents and reaction conditions.

20

Alternatively, they may be prepared according to scheme 19 below, when Het is N-linked:

**Scheme 19.**

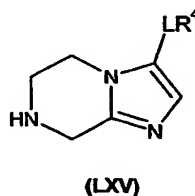
Step (mm): Metalation of compound (LXI) is undertaken with a suitable base (e.g. nBuLi) at low temp. (-78°C), followed by quench with bromine, to give compound (LXII).

- 5 Preferred conditions are: 1.1 eq. nBuLi, in tetrahydrofuran at -78°C for 15 mins, then 1.1 eq. Bromine.

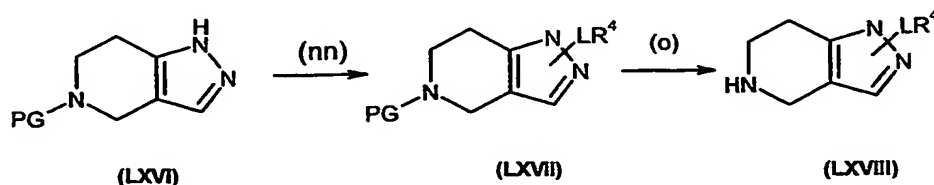
Compound (LXIII) may be obtained by reaction with Het, according to the methods described previously in step yy.

10

Compound (LXIV) may be obtained by reaction of bromide (LXII) with R⁴COH, according to the conditions described previously for step v.



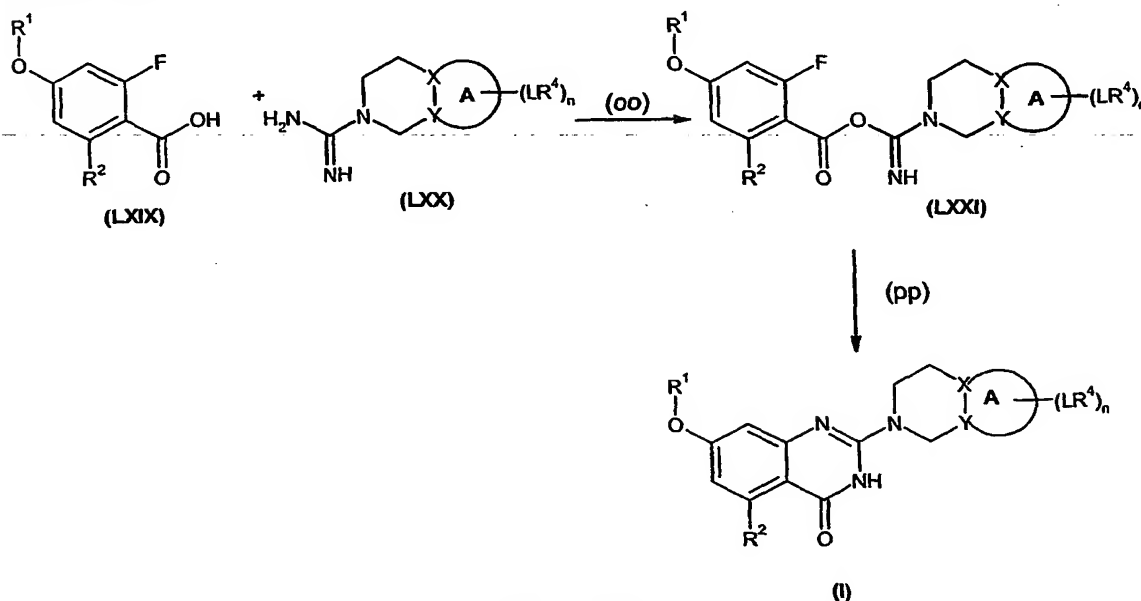
- 15 Compounds of formula (LXV) may be prepared by analogy to the method described in WO 97/30053, and to those described herein, from appropriate aminomethylketones, prepared in accordance with the method of Yinglin and Hongwen, Synthesis 1990; 615, and other readily available starting materials.

**Scheme 20.**

20

- Step (nn) :** Alkylation of compound (LXVI), where PG is a suitable N-protecting group, (preferably Boc or benzyl) is achieved, using a suitable alkylating agent, LR^4 -LG, (where LR^4 is as previously defined, and LG is a suitable leaving group, preferably halo) in the presence of a suitable alkali metal base (e.g. NaOH, K_2CO_3) in a solvent such as N,N-dimethylformamide or MeCN, at elevated temperature. The preferred conditions are: 1.2 eq. ZLG, 3 eq. K_2CO_3 in N,N-dimethylformamide at 65°C for 26 hrs.

Compounds of formula (I) may also be prepared by the method shown in Scheme 21.



Scheme 21.

- Step (oo)** The acyl guanidine (LXXI) may be prepared by using either
- (i) the acid chloride of acid (LXIX) and the anion of the guanidine (LXX) prepared in situ, in the presence of a base such as K^tBuO , NaOH, K_2CO_3 or Cs_2CO_3 in a suitable solvent e.g. DMF, or
 - (ii) the acid (LXIX) with a conventional coupling agent such as CDI or DCC and the guanidine (LXX), in the presence of base such as caesium carbonate in a suitable solvent e.g. DMF.

Typically the conditions are as follows:

- (i) acid chloride of acid (LXIX) (generated in-situ), an excess of guanidine (LXX), with an excess of base such as K^tBuO or NaH, in DMF, without heating for 1 to 24 hrs, or

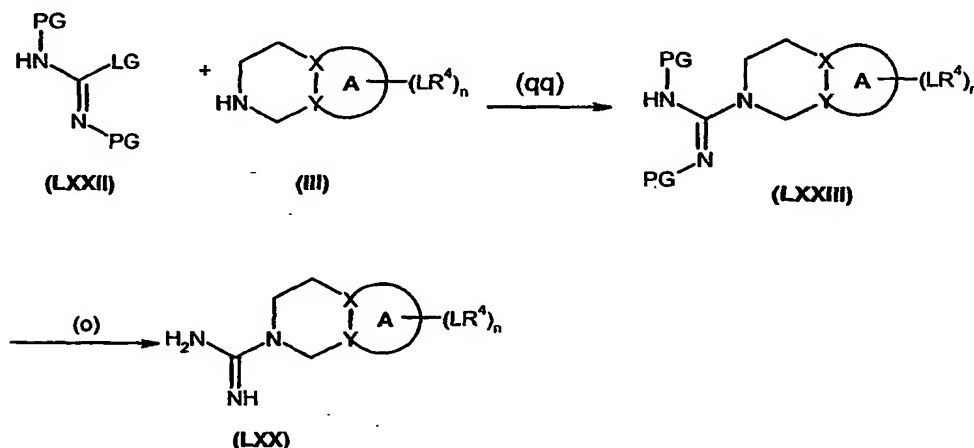
(ii) acid (LXIX), CDI, an excess of guanidine (LXX), with an excess Cs_2CO_3 in DMF, at room temperature for 12 to 48 hrs.

Step (pp) Cyclisation of the acyl guanidine (LXXI) to give compound (I) is accomplished by reaction in the presence of a suitable base such as NaOH or K^tBuO in a suitable high boiling solvent such as 3-methyl-pentan-3-ol or ethylene glycol

Typically the conditions are as follows

The guanidine (LXXI) with excess potassium t-butoxide in 3-methyl-pentan-3-ol under reflux for 1 to 24 hours

- 10 Compounds suitable for use as compound (LXX) may be prepared from appropriate compounds of formula (III) by the methods shown in Scheme 22.



Scheme 22.

- 15 LG is a suitable leaving group such as SH, SMe, pyrazole or NH-triflyl. Preferred is SMe.

PG is a nitrogen protecting group such as CBz or boc. Preferred is boc on both nitrogens

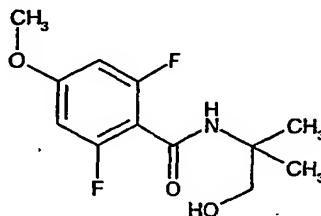
- 20 **Step (qq)** Compound (LXXIII) can be prepared from compounds (LXXII) and (III) by mixing them with a suitable transition metal salt such as mercury (II) chloride or silver chloride in the presence of an excess of tertiary amine base such as Hünig's base or triethylamine in a suitable solvent such as dichloromethane for 1 to 24 hours
- Preferred conditions are; 1.2 eq. of compound (LXXII) 1.2 eq. mercury (II) chloride, 3
- 25 eq. triethylamine in dichloromethane for 16 hours.

It will be appreciated by one skilled in the art that further elaboration of suitable R² groups (for example those containing a "reactive" N atom, which optionally may be part of a ring) may be achieved using standard chemical transformations (for example alkylation, reduction or reductive amination). Furthermore, it will be appreciated that
5 standard protecting and deprotecting group strategies may be employed.

The following preparations describe the preparation of certain intermediate compounds used for the synthesis of compounds of the formula (I):

- 10 Spectroscopic data were recorded on a Finnigan Mat. Navigator (LRMS, either positive (ES⁺) or negative (ES⁻) electrospray mode), and Varian Unity Inova-400 (NMR, 400 MHz) instruments and are consistent with the assigned structures. Optical rotations were obtained using a Perkin Elmer 341 polarimeter.
- 15 Combustion analyses were performed by Exeter Analytical (UK) Limited, Uxbridge, Middlesex. Reactions were performed under an atmosphere of dry nitrogen unless otherwise noted. Flash chromatography refers to column chromatography on silica gel (Kieselgel 60, 230-400 mesh, from E. Merck, Darmstadt). Kieselgel 60 F₂₅₄ plates from E. Merck were used for TLC, and compounds were visualised using UV light, 5%
20 aqueous potassium permanganate or chloroplatinic acid/potassium iodide solution.

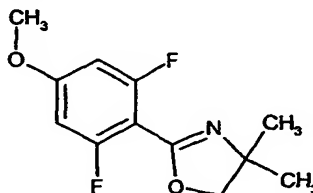
In cases where compounds were analysed as hydrates, the presence of water was evident in the enhanced peak due to water in the NMR spectra. The purity of compounds was carefully assessed using analytical TLC and proton NMR (400 MHz),
25 and the latter was used to calculate the amount of solvent in solvated samples. In multistep sequences, the purity and structure of intermediates were verified spectroscopically by NMR and LRMS.

Preparation 12,6-Difluoro-N-(2-hydroxy-1,1-dimethylethyl)-4-methoxybenzamide

The 2,6-difluoro-4-methoxybenzoic acid (Mol. Cryst. Liq. Cryst. 1989; 172; 165) (2.09g, 11.1mmol) was suspended in dichloromethane (110mL) and a few drops of N,N-dimethylformamide was added followed by oxalyl chloride (2.79g, 22.2mmol). The reaction mixture was stirred for 45 minutes at room temperature, after which time a clear homogeneous solution had formed. The reaction mixture was concentrated under reduced pressure and redissolved in dichloromethane (100mL). The reaction mixture was then added slowly to an ice-cold solution of amino-2-methylpropanol (3.56g, 40mmol), in dichloromethane (50mL). After stirring at room temperature for 1 hour, the reaction mixture was washed with water (75mL), 0.2N hydrochloric acid (50mL), dried (MgSO₄) and concentrated under reduced pressure to give the title compound as a white solid (2.77g, 96%).

¹H-nmr (CDCl₃, 400MHz) δ : 1.38 (s, 6H), 3.70 (m, 2H), 3.80 (s, 3H), 5.90 (bs, 1H), 6.42 (2xs, 2H).

LRMS: m/z (ES⁺) 260 [MH⁺]

Preparation 22-(2,6-Difluoro-4-methoxyphenyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole

To a solution of the alcohol from preparation 1 (2.75g, 10.6mmol) in anhydrous dichloromethane (50mL) was added thionyl chloride (1.43g, 12mmol) and the reaction stirred for 1.5 hours at room temperature. The reaction mixture was poured into 1M sodium hydroxide solution (50mL) and extracted with dichloromethane (2 x 50mL). The combined organic solutions were dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting

with dichloromethane:methanol 96:4) to give the title compound as a clear oil (2.40g, 94%).

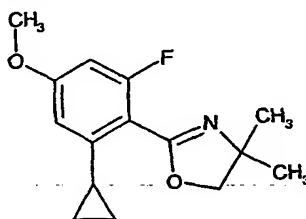
$^1\text{H-nmr}$ (CDCl_3 , 400MHz) δ : 1.40 (s, 6H), 3.80 (s, 3H), 4.04 (s, 2H), 6.42 (m, 2H).

LRMS: m/z (ES^+) 242 [MH^+]

5

Preparation 3

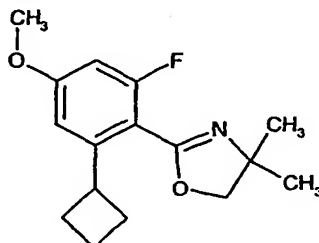
2-(2-Cyclopropyl-6-fluoro-4-methoxyphenyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole



To a solution of cyclopropyl bromide (12.1g, 100mmol) in anhydrous tetrahydrofuran (100mL) was added magnesium turnings (2.4g, 100mmol) followed by a crystal of iodine, at room temperature. After a few minutes the reaction initiated and came to reflux without any additional heating. When the reflux was complete the reaction was cooled to room temperature and stirred for 2 hours. A solution of the fluoro compound from preparation 2 (9.64g, 40mmol) in tetrahydrofuran (50mL) was cooled in an ice-bath to 0°C, and the grignard solution (50mL) was added dropwise over 15 minutes, the cooling bath was removed and reaction warmed to room temperature and stirred for 1 hour. Further grignard solution (20mL) was added and stirred for 1 hour. Further grignard solution (10mL) was added and stirred for 1 hour. The reaction mixture was then quenched with 1M citric acid (30mL), as some solid remained undissolved 2M hydrochloric acid (30mL) was added. The resultant mixture was partitioned between ethyl acetate (400mL) and water (200mL), basified with concentrated ammonia solution and the organic layer separated, washed with water (150mL), brine (150mL), dried (MgSO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluting with hexane:isopropyl alcohol 85:15) to give the title compound as a clear oil (10.32g, 98%).

$^1\text{H-nmr}$ (CDCl_3 , 400MHz) δ : 0.66 (m, 2H), 0.94 (m, 2H), 1.40 (s, 6H), 2.18 (m, 1H), 3.78 (s, 3H), 4.07 (s, 2H), 6.25 (s, 1H), 6.42 (m, 1H).

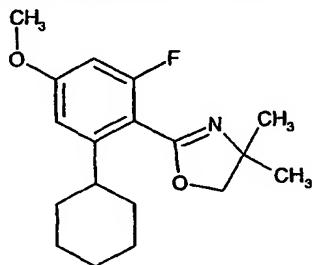
LRMS : m/z (ES^+) 286 [MNa^+]

Preparation 42-(2-Cyclobutyl-6-fluoro-4-methoxyphenyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole

To a solution of cyclobutyl chloride (5.64g, 62mmol) in anhydrous tetrahydrofuran (60mL) was added magnesium turnings (1.56g, 65mmol) followed by a crystal of iodine, at room temperature. The mixture was stirred at room temperature for 1 hour, followed by a further hour under reflux. A solution of the fluoro compound from preparation 2 (7.23g, 30mmol) in tetrahydrofuran (80mL) was cooled in an ice-bath to 0°C, and the grignard solution (40mL) was added dropwise over 15 minutes, the cooling bath was removed and reaction warmed to room temperature and stirred for 2 hours. Further grignard solution (10mL) was added and the reaction stirred for a further 30 minutes. The reaction was poured into a solution of ethylenediaminetetraacetic acid disodium salt (12g) in 1N sodium hydroxide (100mL), and the mixture extracted with ethyl acetate (1x200mL, 2x100mL). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure, to afford the title compound as a pale yellow oil, 8.31g.

¹H-nmr (CDCl₃, 40MHz) δ: 1.43 (s, 6H), 1.77-1.88 (m, 1H), 1.91-2.07 (m, 1H), 2.07-2.20 (m, 2H), 2.24-2.36 (m, 2H), 3.82 (s, 3H), 3.83 (m, 1H), 4.10 (s, 2H), 6.48 (dd, 1H), 6.66 (d, 1H).

LRMS: m/z (APCI⁺) 278 [MNH₄⁺]

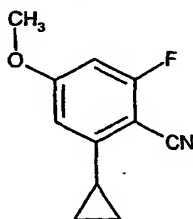
Preparation 52-(2-Cyclohexyl-6-fluoro-4-methoxyphenyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole

Cyclohexylmagnesium chloride (22mL, 2M in diethyl ether, 44mmol) was added slowly
5 to an ice-cooled solution of the compound from preparation 2 (9.64g, 40mmol) in tetrahydrofuran (100mL), and the solution then stirred at room temperature for 2 hours. Water (10mL) was added, the mixture poured into ethyl acetate, and washed with a solution of ethylenediaminetetracetic acid disodium salt (24g) in water (200mL), then 1N sodium hydroxide solution (100mL) and brine. The organic solution was dried
10 (MgSO₄) and evaporated under reduced pressure to afford the title compound as a colourless oil, 12.4g.

¹H-nmr (CDCl₃, 400MHz) δ: 1.15-1.50 (m, 10H), 1.76 (d, 2H), 1.84 (m, 2H), 1.90 (m, 2H), 2.86 (m, 1H), 3.80 (s, 3H), 4.13 (s, 2H), 6.47 (dd, 1H), 6.63 (d, 1H).

LRMS: m/z (APCI⁺) 306 [MH⁺]

15

Preparation 62-Cyclopropyl-6-fluoro-4-methoxybenzonitrile

Pyridine (31.6g, 400mmol) was added to a solution of the compound from preparation
20 3 (10.32g, 39.2mmol) in ethyl acetate (150mL), followed by phosphorous oxychloride (12.27g, 80mmol). The reaction was stirred at reflux for 5 hours, cooled and poured onto ice. This aqueous mixture was extracted with ethyl acetate, the organic solution washed with 2M hydrochloric acid, and brine then dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel
25 using dichloromethane to afford the title compound as a white solid, 6.41g.

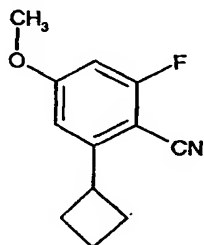
¹H-nmr (CDCl₃, 400MHz) δ: 0.88 (m, 2H), 1.16 (m, 2H), 2.20 (m, 1H), 3.80 (s, 6H), 6.21 (s, 1H), 6.49 (m, 1H).

LRMS: m/z (ES⁺) 214 [MNa⁺]

5

Preparation 7

2-Cyclobutyl-6-fluoro-4-methoxybenzonitrile



The title compound was obtained as a pale yellow oil in 99% yield from the compound from preparation 4, following a similar procedure to that described in preparation 6, except the compound was isolated without column chromatography.

10

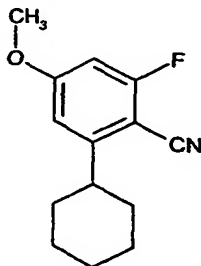
¹H-nmr (CDCl₃, 400MHz) δ: 1.78-1.94 (m, 1H), 1.99-2.24 (m, 3H), 2.41-2.55 (m, 2H), 3.81 (m, 1H), 3.87 (s, 3H), 6.53 (dd, 1H), 6.69 (d, 1H).

LRMS: m/z (APCI⁺) 223 [MNH₄⁺]

15

Preparation 8

2-Cyclohexyl-6-fluoro-4-methoxybenzonitrile

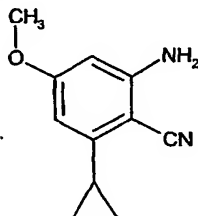


The title compound was obtained as a colourless oil in 93% yield from the compound from preparation 5, following a similar procedure to that described in preparation 6.

¹H-nmr (CDCl₃, 400MHz) δ: 1.18-1.57 (m, 4H), 1.73-1.96 (m, 6H), 2.85-2.96 (m, 1H), 3.85 (s, 3H), 6.54 (dd, 1H), 6.65 (d, 1H).

20

LRMS: m/z (APCI⁺) 251 [MNH₄⁺]

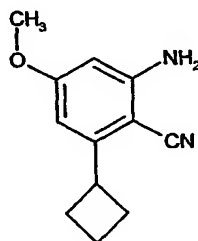
Preparation 92-Amino-6-cyclopropyl-4-methoxybenzonitrile

5 The fluoro compound from preparation 6 (3.0g, 15.7mmol) was added to a saturated solution of 0.88 ammonia in dimethylsulphoxide (20mL), and the solution stirred in a sealed vessel for 18 hours at 150°C. The cooled mixture was partitioned between ethyl acetate and water and the layers separated. The organic phase was dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using dichloromethane as eluant to afford the title compound as a white crystalline solid, 1.28g.

10 ¹H-nmr (CDCl₃, 400MHz) δ: 0.74 (m, 2H), 1.02 (m, 2H), 2.10 (m, 1H), 3.76 (s, 6H), 4.38 (bs, 2H), 5.82 (s, 1H), 6.00 (s, 1H).

LRMS: m/z (ES⁺) 211 [MNa⁺]

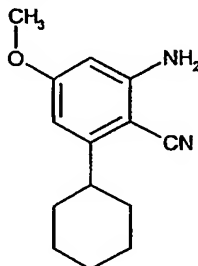
15

Preparation 102-Amino-6-cyclobutyl-4-methoxybenzonitrile

20 The title compound was obtained as a white solid in 54% yield from the fluoro compound from preparation 7, following a similar procedure to that described in preparation 9, except dichloromethane:ethyl acetate (100:0 to 80:20) was used as the column eluant.

¹H-nmr (CDCl₃, 400MHz) δ: 1.76-1.90 (m, 1H), 1.94-2.21 (m, 3H), 2.37-2.49 (m, 2H), 3.66-3.77 (m, 1H), 3.80 (s, 3H), 4.06-4.43 (bs, 2H), 6.05 (s, 1H), 6.27 (s, 1H).

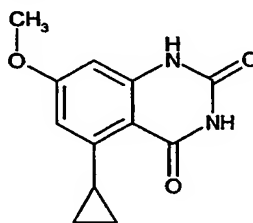
25 LRMS: m/z (ES⁺) 225 [MNa⁺]

Preparation 112-Amino-6-cyclohexyl-4-methoxybenzonitrile

The title compound was obtained as a yellow solid in 44% yield from the fluoro compound from preparation 8, following the procedure described in preparation 9.

¹H-nmr (CDCl₃, 400MHz) δ: 1.17-1.53 (m, 5H), 1.72-1.96 (m, 5H), 2.80 (m, 1H), 3.78 (s, 3H), 6.05 (d, 1H), 6.22 (d, 1H).

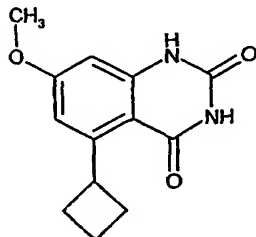
LRMS: m/z (APCI⁺) 231 [MH⁺]

Preparation 125-Cyclopropyl-7-methoxy-2,4(1H,3H)-quinazolinedione

A solution of the compound from preparation 9 (1.25g, 6.65mmol) in N,N-dimethylformamide (10mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (2mL) was cooled to -78°C, and solid carbon dioxide added. The reaction vessel was sealed and heated to 140°C for 18 hours. The cooled mixture was poured into water (150mL), then acidified using 2N hydrochloric acid, and the mixture stirred for 10 minutes. The resulting precipitate was filtered off, washed with water and acetone, to afford the title compound as a white solid, 1.44g.

¹H-nmr (DMSO-d₆, 400MHz) δ: 0.68 (m, 2H), 0.95 (m, 2H), 3.40 (m, 1H), 3.76 (s, 3H), 6.18 (s, 1H), 6.42 (s, 1H).

LRMS: m/z (ES⁻) 231 [M-H]

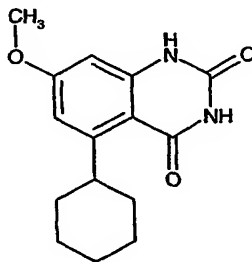
Preparation 135-Cyclobutyl-7-methoxy-2,4(1H,3H)-quinazolinedione

5 The title compound was obtained as an off-white solid in 75% yield, from the compound from preparation 10, following the procedure described in preparation 12.

¹H-nmr (DMSOd₆, 400MHz) δ: 1.72 (m, 1H), 1.81-2.05 (m, 3H), 2.29 (m, 2H), 3.81 (s, 3H), 4.45 (m, 1H), 6.50 (d, 1H), 6.62 (d, 1H), 10.79 (s, 1H), 10.85 (s, 1H).

LRMS: m/z (APCI⁺) 245 [M-H⁺]

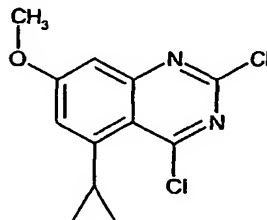
10

Preparation 145-Cyclohexyl-7-methoxy-2,4(1H,3H)-quinazolinedione

The title compound was obtained as a white solid in 77% yield, from the compound from preparation 11, following the procedure described in preparation 12.

15 ¹H-nmr (DMSOd₆, 400MHz) δ: 1.14-1.45 (m, 5H), 1.63-1.82 (m, 5H), 3.78 (s, 3H), 4.08 (t, 1H), 6.50 (d, 1H), 6.58 (d, 1H), 10.80 (s, 1H), 10.85 (s, 1H).

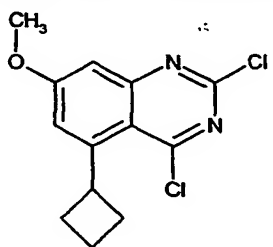
LRMS: m/z (APCI⁺) 273 [M-H⁺]

Preparation 152,4-Dichloro-5-cyclopropyl-7-quinazolinyl methyl ether

To a solution of the compound from preparation 12 (3.87g, 16.7mmol) in phosphorous
5 oxychloride (50mL) was added N,N-diisopropylethylamine (5.17g, 40mmol). The
reaction mixture was heated at 100°C for 1 hour, at reflux for 6 hours then cooled to
room temperature. The phosphorous oxychloride was removed under reduced
pressure. The resultant oil was partitioned between ethyl acetate (500mL) and ice-
water (300mL), the layers were separated, the organic phase washed with 1M
10 hydrochloric acid (100mL), brine (100mL), dried (MgSO₄) and concentrated under
reduced pressure. The residue was purified by column chromatography on silica gel
eluting with a solvent gradient of dichloromethane:ethyl acetate (100:0 to 94:6) to give
the title compound as a white solid (3.97g, 88%).

¹H-nmr (CDCl₃, 400MHz) δ: 0.84 (m, 2H), 1.17 (m, 2H), 2.70 (m, 1H), 2.94 (s, 3H), 7.10
15 (s, 1H), 7.14 (s, 1H).

LRMS: m/z (ES⁺) 291 [MNa⁺]

Preparation 162,4-Dichloro-5-cyclobutyl-7-quinazolinyl methyl ether

20

To a solution of the compound from preparation 13 (2.46g, 10mmol) in phosphorous
oxychloride (25mL) was added N,N-diisopropylethylamine (3.1g, 24mmol) and the
reaction mixture was heated at reflux for 7 hours then cooled to room temperature.
The solution was poured cautiously onto ice, diluted with water, and the mixture
25 extracted with dichloromethane (3x100mL). The combined organic solutions were dried
(MgSO₄) and concentrated under reduced pressure. The residue was purified by

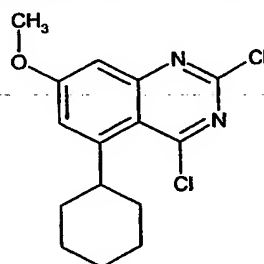
column chromatography on silica gel eluting with a solvent gradient of dichloromethane:ethyl acetate (100:0 to 94:6) to give the title compound as a white solid, 1.74g.

¹H-nmr (CDCl₃, 400MHz) δ: 1.84-1.94 (m, 1H), 2.00-2.23 (m, 3H), 2.49-2.60 (m, 2H),
5 3.97 (s, 3H), 4.60 (m, 1H), 7.14 (d, 1H), 7.27 (d, 1H).

LRMS: m/z (ES⁺) 305 [MNa⁺]

Preparation 17

2,4-Dichloro-5-cyclohexyl-7-methoxy quinazolinyl methyl ether



10

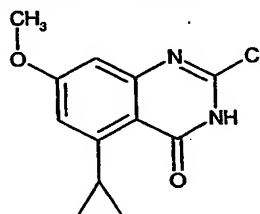
The title compound was obtained as a white solid in 64% yield, from the compound from preparation 14, following the procedure described in preparation 16.

¹H-nmr (CDCl₃, 400MHz) δ: 1.21-1.60 (m, 5H), 1.73-2.07 (m, 5H), 3.96 (s, 3H), 4.05 (m, 1H), 7.16 (d, 1H), 7.23 (d, 1H).

15 LRMS: m/z (APCI⁺) 311 [MH⁺]

Preparation 18

2-Chloro-5-cyclopropyl-7-methoxy-4(3H)-quinazolinone



20 1N Sodium hydroxide solution (30mL) was added to a solution of the chloro compound from preparation 15 (2.2g, 8.18mmol) in dioxane (50mL) and the reaction stirred at room temperature for 2 hours. The reaction was acidified using 2M hydrochloric acid and extracted with dichloromethane:methanol (95:5) (3x150mL). The combined organic solutions were dried (MgSO₄) and evaporated under reduced pressure to give the title
25 compound as a white solid, 1.85g.

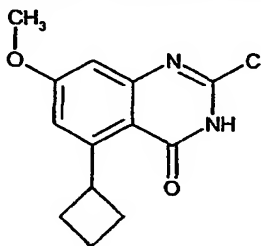
^1H -nmr (CDCl_3 , 400MHz) δ : 0.73 (m, 2H), 1.09 (m, 2H), 3.31 (m, 1H), 3.86 (s, 3H), 6.60 (d, 1H), 6.89 (d, 1H).

LRMS: m/z (ES^+) 273 [MNa^+]

5

Preparation 19

2-Chloro-5-cyclobutyl-7-methoxy-4(3H)-quinazolinone



2M Sodium hydroxide solution (12.5mL, 25mmol) was added to a solution of the dichloride from preparation 16 (1.71g, 6.04mmol) in dioxane (50mL), and the solution stirred at room temperature for 8 hours. The mixture was acidified using 2M hydrochloric acid (20mL), the resulting precipitate filtered off, washed with water, acetone and diethyl ether, and dried *in vacuo*, to afford the title compound, 1.26g.

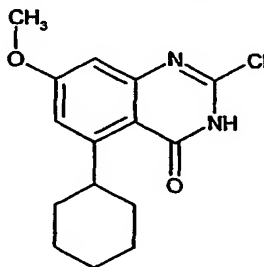
^1H -nmr (DMSO-d_6 , 400MHz) δ : 1.69-1.79 (m, 1H), 1.86-2.10 (m, 3H), 2.27-2.38 (m, 2H), 3.87 (s, 3H), 4.51 (m, 1H), 6.90 (d, 1H), 6.94 (d, 1H), 12.83 (bs, 1H).

LRMS: m/z (ES^+) 287 [MNa^+]

15

Preparation 20

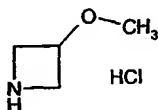
2-Chloro-5-cyclohexyl-7-methoxy-4(3H)-quinazolinone



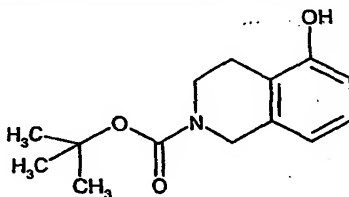
The title compound was obtained as a white solid in 96% yield, after trituration with diethyl ether, from the dichloride from preparation 17, following a similar procedure to that described in preparation 18.

^1H -nmr (DMSO-d_6 , 400MHz) δ : 1.14-1.47 (m, 5H), 1.66-1.84 (m, 5H), 3.85 (s, 3H), 4.13 (m, 1H), 6.88 (d, 1H), 6.90 (d, 1H), 12.84 (bs, 1H). LRMS: m/z (ES^+) 293 [MH^+]

25

Preparation 213-Methoxyazetidine hydrochloride

- 1N Ethereal hydrochloric acid was added to a solution of 1-(diphenylmethyl)-3-methoxyazetidine (WO 9613502) (1.3g, 5.14mmol) in dichloromethane (10mL), until a precipitate formed, and the mixture evaporated under reduced pressure. The residual foam was re-dissolved in methanol (75mL), 10% palladium on charcoal (900mg) and ammonium formate (6.5g) added, and the mixture heated under reflux for 30 minutes. The cooled mixture was filtered through Arbocel®, the filtrate evaporated under reduced pressure, and the residue partitioned between dichloromethane and water. The layers were separated, the aqueous phase acidified using 1N hydrochloric acid, and the solution evaporated under reduced pressure. The residual solid was triturated with ethanol and then dichloromethane, and the solid filtered off. The filtrate was evaporated under reduced pressure to give the title compound as a yellow oil, 130mg.
- ¹H-nmr (CDCl₃, 400MHz) δ: 3.22 (bs, 3H), 3.88 (m, 2H), 4.10 (m, 2H), 4.26 (m, 1H).

Preparation 22tert-Butyl 5-hydroxy-3,4-dihydro-2(1H)-isoquinolinecarboxylate

- A solution of di-tert-butyl dicarbonate (66.75g, 0.31mol) was suspended in 1M sodium hydroxide solution (200mL) and 1,4-dioxane (300mL) under nitrogen gas. A solution of 1,2,3,4-tetrahydro-5-isoquinolinol (20.0g, 134mmol) in 1,4-dioxane (100mL) was added and the resulting suspension stirred at room temperature for 16 hours. The reaction mixture was concentrated under reduced pressure, and the residue partitioned between 1M hydrochloric acid (300mL) and dichloromethane (500mL). The aqueous phase was re-extracted with dichloromethane (200mL). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure to give an orange oil. The crude product was dissolved in 1,4-dioxane (200mL) and methanol (100mL) under nitrogen gas followed by the addition of 2N sodium hydroxide solution (150mL) and the resulting cloudy mixture was stirred at room temperature for 3 hours. The reaction

mixture was concentrated under reduced pressure, and the residue partitioned between ethyl acetate (600mL) and water (200mL). The organic phase was separated, washed with 2N hydrochloric acid (200mL), brine (250mL) then dried (MgSO₄) and concentrated under reduced pressure to give a tan solid. The solid was suspended in dichloromethane (150mL) then pentane added (800mL) and filtered to give the title compound as a white solid (32.04g, 84%).

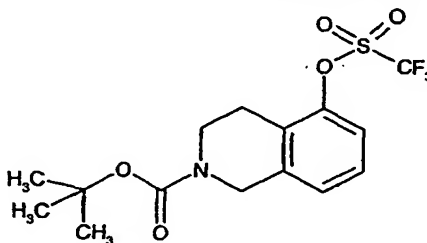
¹H-nmr (CDCl₃, 300MHz) δ: 1.49 (s, 9H), 2.76 (t, 2H), 3.66 (t, 2H), 4.56 (s, 2H), 5.29 (bs, 1H), 6.67 (dd, 2H), 7.05 (dd, 1H).

LRMS: m/z (ES⁺) 272 [MNa⁺].

Microanalysis: Found: C, 67.30; H, 7.68; N, 5.61. C₁₄H₁₉NO₃ requires C, 67.45; H, 7.68; N, 5.62 %

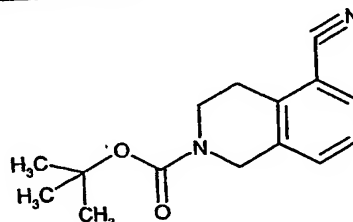
Preparation 23

tert-Butyl 5-[[[(trifluoromethyl)sulfonyl]oxy]-3,4-dihydro-2(1H)-isoquinolinecarboxylate



Triethylamine (20.1mL, 144mmol) was added to a suspension of the compound from preparation 22 (32.65g, 131mmol) in dichloromethane (400mL) under nitrogen gas. The mixture was cooled to 0°C and N-phenylbistrifluoromethanesulfonamide (51.46g, 144mmol) was added portionwise. The resulting brown solution was allowed to warm to room temperature and stirred for 16 hours. The reaction mixture was washed consecutively with water (200mL), 0.5M hydrochloric acid (200mL), brine (250mL) and then dried (MgSO₄) and concentrated under reduced pressure to give a brown oil. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient of n-pentane:diethyl ether (100:0 to 70:30). The product was co-evaporated with dichloromethane (2 x 100mL) to give the title compound as a colourless gum (40.1g, 80%).

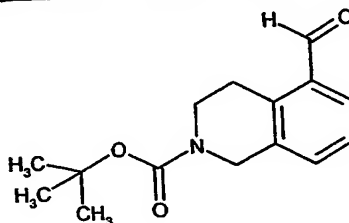
¹H-nmr (CDCl₃, 300MHz) δ: 1.49 (s, 9H), 2.89 (t, 2H), 3.65 (t, 2H), 4.59 (s, 2H), 7.13 (m, 2H), 7.24 (dd, 1H). LRMS : m/z (ES⁺) 404 [MNa⁺].

Preparation 24tert-Butyl 5-cyano-3,4-dihydro-2(1H)-isoquinolinecarboxylate

The compound from preparation 23 (20.0g, 52mmol) was dissolved in N,N-dimethylformamide (120mL) under nitrogen gas. Zinc cyanide (6.15g, 52mmol), lithium chloride (2.22g, 52mmol) and tetrakis(triphenylphosphine)palladium (0) (2.42g, 2.1mmol) were added and the mixture heated at 110°C for 8 hours. The reaction mixture was concentrated under reduced pressure, and the residue partitioned between dichloromethane (500mL) and saturated sodium bicarbonate solution (250mL). The aqueous phase was re-extracted with dichloromethane (300mL). The combined organic solutions were dried (MgSO₄) and concentrated under reduced pressure to give a golden oil. The crude product was purified by column chromatography on silica gel using n-pentane:ethyl acetate (90:10) as eluant. The product was co-evaporated with dichloromethane (2 x 100mL) to give the title compound as a colourless oil (13.32g, 49%).

¹H-nmr (CDCl₃, 300MHz) δ: 1.48 (s, 9H), 3.02 (t, 2H), 3.70 (t, 2H), 4.58 (s, 2H), 7.20-7.35 (m, 2H), 7.50 (d, 1H).

LRMS : m/z (ES⁺) 281 [MNa⁺].

Preparation 25tert-Butyl 5-formyl-3,4-dihydro-2(1H)-isoquinolinecarboxylate

A solution of the compound from preparation 24 (9.1g, 35mmol) in toluene (100mL) was cooled to -78°C under nitrogen gas. Over 1 hour, diisobutylaluminium hydride (80 mL of a 1M solution in toluene, 80 mmol) was added dropwise keeping the internal temperature below -60°C and the resulting mixture stirred for 2 hours at -78°C. Methanol (20mL) was pre-cooled to -78°C and the added dropwise to the reaction

mixture keeping the internal temperature below -60°C. Over 20 mins the reaction mixture was poured into 1N hydrochloric acid (200mL) that had been pre-cooled to 0°C. The reaction mixture was extracted with ethyl acetate (3 x 400mL) and the combined organic extracts were washed with brine (200mL), dried (MgSO₄) and concentrated under reduced pressure. The product was co-evaporated with dichloromethane (2 x 50mL) to give the title compound as a yellow oil (8.14g, 88%).

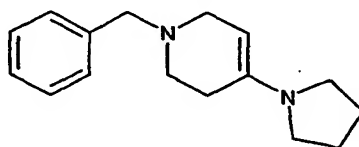
¹H-nmr (DMSO-d₆, 400MHz) δ: 1.40 (s, 9H), 3.19 (t, 2H), 3.55 (t, 2H), 4.55 (s, 2H), 7.40 (dd, 2H), 7.47 (d, 1H), 7.70 (d, 1H).

LRMS : m/z (ES⁺) 284 [MNa⁺].

10

Preparation 26

1-Benzyl-4-(1-pyrrolidinyl)-1,2,3,6-tetrahydropyridine



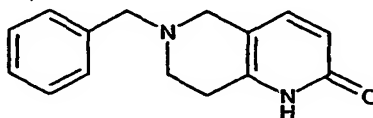
Pyrrolidine (31.8mL, 0.38mol) was added to a solution of 1-benzyl-4-piperidinone (48.0g, 0.25mol) in toluene (180mL) and the mixture refluxed under Dean-Stark conditions for 4.5 hours. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure to give the title compound as an orange oil (61.8g, 100%).

¹H-nmr (400MHz, CDCl₃) δ: 1.80-1.84 (m, 4H), 2.32 (m, 2H), 2.59 (t, 2H), 3.02 (4Hm,), 3.07 (s, 2H), 3.57 (s, 2H), 4.18 (s, 1H), 7.22-7.30 (m, 3H), 7.35-7.36 (d, 2H).

20

Preparation 27

6-Benzyl-5,6,7,8-tetrahydro[1,6]naphthyridin-2(1H)-one



A mixture of the compound from preparation 26 (61.50g, 0.25mol) and propiolamide (J. Am. Chem. Soc. 1988; 110; 3968) (35.05g, 0.51mol) were heated under reflux in toluene (500mL) under nitrogen gas for 16 hours. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was partitioned between dichloromethane (800mL) and saturated sodium bicarbonate solution (400mL). The aqueous phase was further extracted with dichloromethane (3 x

30

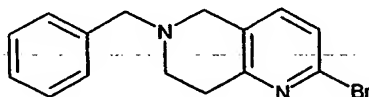
500mL). The combined organic solutions were dried (MgSO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a solvent gradient of dichloromethane:methanol (100:0 to 95:05) to give the title compound as an orange solid (27.71g, 45%).

- 5 ^1H -nmr (DMSO-d_6 , 400MHz) δ : 2.53 (t, 2H), 2.63 (t, 2H), 3.24 (s, 2H), 3.60 (s, 2H), 6.06 (d, 1H), 7.08 (d, 1H), 7.24 (m, 1H), 7.30 (m, 4H).
LRMS : m/z (ES^+) 263 [MNa^+].

Preparation 28

10

6-Benzyl-2-bromo-5,6,7,8-tetrahydro[1,6]naphthyridine

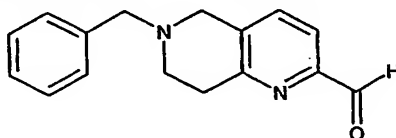


- The compound from preparation 27 (9.51g, 31mmol) was suspended in acetonitrile (45mL) and anisole (45mL). Phosphorous oxybromide (44.8g, 156mmol) was added portionwise and the mixture heated for 1 hour at 120°C. The reaction was allowed to cool to room temperature and then poured onto ice (400g). Dichloromethane (400mL) was added and the mixture was then neutralised with saturated sodium carbonate solution (450mL). The organic layer was collected and the aqueous layer extracted with dichloromethane (500mL). The combined organic solutions were dried (MgSO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a solvent gradient of dichloromethane:methanol (100:0 to 97:03) to give the title compound as a brown oil (5.79g, 61%).

- 15 ^1H -nmr (CDCl_3 , 400MHz) δ : 2.83 (t, 2H), 3.03 (t, 2H), 3.56 (s, 2H), 3.70 (s, 2H), 7.12 (d, 1H), 7.21 (d, 1H), 7.26-7.36 (m, 5H).
20 LRMS : m/z (ES^+) 303 [MH^+].
25

Preparation 29a

6-Benzyl-5,6,7,8-tetrahydro[1,6]naphthyridine-2-carbaldehyde



- 30 The bromide from preparation 28 (3.00g, 9.90mmol) was dissolved in tetrahydrofuran (70mL) and cooled to -78°C. n-Butyl lithium (5.5mL as a 2.5M solution in hexanes,

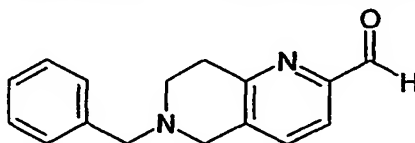
13.8mmol) was added and the reaction stirred for a 5 minutes. N,N-Dimethylformamide (2.3mL, 29.7mmol) was then added and the reaction stirred for 1 hour, the cooling bath removed and the reaction quenched by the addition of saturated potassium dihydrogenphosphate solution (100mL). The residue was purified by flash chromatography on silica gel eluting with dichloromethane : methanol (98:2) to give the title compound as a tan solid (2.10g, 85%).

¹H-nmr (DMSO-d₆, 400MHz) δ: 2.92 (m, 2H), 3.15 (m, 2H), 3.71 (s, 2H), 3.75 (s, 2H), 7.26-7.38 (m, 5H), 7.45 (d, 1H), 7.73 (d, 1H), 10.02 (s, 1H).

LRMS : m/z (ES⁺) 275 [MNa⁺].

Preparation 29b

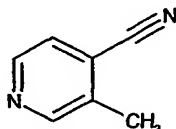
6-Benzyl-5,6,7,8-tetrahydro[1,6]naphthyridine-2-carbaldehyde



A solution of sodium periodate (4.38 g, 20.5 mmol) in water (38 ml) was added dropwise to a solution of the diol from preparation 154 (7.2 g, 18.7 mmol) in acetonitrile (200 ml), and the reaction was stirred at room temperature for 2 hours. The mixture was partitioned between ethyl acetate (300 ml) and water (300 ml), containing a small volume of brine, and the layers separated. The aqueous phase was further extracted with ethyl acetate (2x100 ml), and the combined organic solutions dried over magnesium sulphate and concentrated under reduced pressure, co-evaporating with tetrahydrofuran. The residual oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane: ethyl acetate (80:20 to 50:50) to afford the title compound, as an oil that crystallised on standing (1.3g).

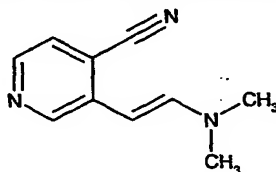
¹H-nmr (CDCl₃, 400MHz) δ: 2.90 (t, 2H), 3.16 (t, 2H), 3.69 (s, 2H), 3.74 (s, 2H), 7.23-7.39 (m, 5H), 7.42 (d, 1H), 7.72 (d, 1H), 10.00 (s, 1H).

LRMS: m/z (ES⁺) 275 [MNa⁺]

Preparation 303-Methylisonicotinonitrile

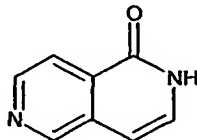
To a solution of 3-picoline N-oxide (60g, 0.55mol) in dichloromethane (1000mL) was
5 added ethyl iodide (132mL, 1.65mol) and the mixture stirred at room temperature for 16
hours. The precipitate was collected by filtration and washed with diethyl ether
(200mL) to give a white solid. The solid was dissolved in water (600mL) and warmed to
50°C. Sodium cyanide (50g, 1.02mol) was added as a solution in water (180mL) over 1
hour, keeping the internal temperature below 60°C and the resulting dark brown
10 solution was stirred at 55°C for a further 1 hour. The reaction mixture was extracted
with diethyl ether (3 x 600mL). The combined organic extracts were dried (MgSO₄) and
concentrated under reduced pressure to give a brown oil. The crude product was
purified by column chromatography on silica gel eluting with a solvent gradient of n-
pentane:dichloromethane (40:60 to 0:100). The product was co-evaporated with
15 dichloromethane (2 x 300mL) to give the title compound as a colourless oil (30.5g,
47%).

¹H-nmr (CDCl₃, 400MHz) δ: 2.55 (s, 3H), 7.47 (d, 1H), 8.60 (d, 1H), 8.67 (s, 1H).

Preparation 313-[(E)-2-(Dimethylamino)ethenyl]isonicotinonitrile

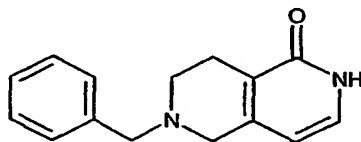
A mixture of the nitrile from preparation 30 (30.49g, 0.26mol) in N,N-dimethylformamide
dimethyl acetal (200mL) and N,N-dimethylformamide (200mL) under nitrogen gas was
heated under reflux for 16 hours. The reaction mixture was concentrated under
25 reduced pressure to give a brown solid. The crude product was dissolved in
dichloromethane (100mL) and n-pentane added until a precipitate formed. The solid
was collected by filtration, washed with n-pentane and dried under reduced pressure to
give the title compound as a green solid (25.1g, 56%).

¹H-nmr (CDCl₃, 400MHz) δ: 2.95 (s, 6H), 5.23 (d, 1H), 7.24 (d, 1H), 8.15 (d, 1H), 8.70
30 (s, 1H). LRMS : m/z (ES⁺) 174 [MH⁺]

Preparation 32[2,6]Naphthyridin-1(2H)-one

48% Hydrobromic acid (97mL, 578mmol) was added over 20 minutes, to a solution of the compound from preparation 31 (10.0g, 57.8mmol) in ethanol (100mL), and the reaction heated under reflux for 18 hours. The cooled mixture was filtered, and the collected solid was washed with ethanol (25mL), and dried *in vacuo*, to afford the title compound as fine yellow crystals, 8.54g.

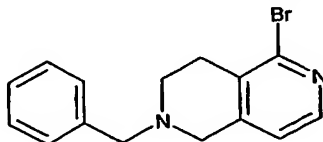
¹H-nmr (DMSOd₆, 400MHz) δ: 6.65 (d, 1H), 7.30 (d, 1H), 7.98 (d, 1H), 8.60 (d, 1H), 9.06 (s, 1H), 11.60 (bs, 1H). LRMS : m/z (ES⁺) 147.5 [MH⁺]

Preparation 336-Benzyl-5,6,7,8-tetrahydro[2,6]naphthyridin-1(2H)-one

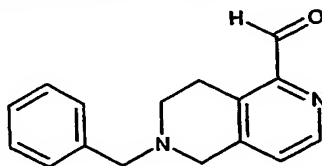
To a suspension of the compound from preparation 32 (20.0g, 0.14mol) in acetonitrile (350mL) under nitrogen gas was added benzyl bromide (24.4mL, 0.21mol) and the reaction heated under reflux for 2 hours. After the reaction mixture had cooled to room temperature it was concentrated under reduced pressure to give a brown oil which was re-dissolved in ethanol (500mL). This solution was cooled to 0°C and sodium borohydride (25.9g, 0.69mol) added portionwise over 30 min and then stirred at 0°C for 1 hour, followed by stirring at room temperature for a further 16 hours. The reaction mixture was cooled to 0°C and 6M hydrochloric acid (200mL) was added dropwise over 30 minutes and then stirred at room temperature for 90 minutes. The resulting precipitate was filtered off, and the aqueous filtrate was basified with 2M sodium hydroxide (1000mL). With stirring, ethyl acetate (250mL) and then cyclohexane (250mL) were added and the resulting precipitate collected by filtration to give the title compound as a light yellow solid (15.50g, 53%).

¹H-nmr (DMSOd₆, 400MHz) δ: 2.27 (t, 2H), 2.60 (t, 2H), 3.28 (s, 2H), 3.62 (s, 2H), 5.87 (d, 1H), 7.10 (d, 1H), 7.21-7.25 (m, 5H), 11.23 (bs, 1H).

LRMS : m/z (ES⁺) 241 [MH⁺].

Preparation 342-Benzyl-5-bromo-1,2,3,4-tetrahydro[2,6]naphthyridine

- Phosphorous oxybromide (74.57g, 260mmol) was added portionwise to a suspension of the compound from preparation 33 (15.5g, 64.6mmol) anisole (200mL) and acetonitrile (100mL), and the solution stirred under reflux for 4 hours. The cooled mixture was poured onto ice (500g) and diluted with dichloromethane (500mL). The mixture was slowly neutralised using saturated sodium bicarbonate solution, the phase separated, and the aqueous layer extracted with further dichloromethane (500mL). The combined organic solutions were dried (MgSO₄) and evaporated under reduced pressure to give a green oil. The crude product as purified by column chromatography on silica gel using an elution gradient of ethyl acetate:pentane (50:50 to 60:40), and repeated using diethyl ether:pentane (50:50) to afford the title compound as a white solid, 17.4g.
- ¹H-nmr (CDCl₃, 400MHz) δ : 2.79 (m, 4H), 3.55 (s, 2H), 3.67 (s, 2H), 6.85 (d, 1H), 7.23-7.33 (m, 5H), 8.06 (d, 1H).
- LRMS : m/z (ES⁺) 326 [MNa⁺]

Preparation 356-Benzyl-5,6,7,8-tetrahydro[2,6]naphthyridine-1-carbaldehyde

- The compound from preparation 34 (3.2g, 10.6mmol) was dissolved in dry tetrahydrofuran (80mL) under nitrogen gas and cooled to -78°C. n-Butyl lithium (7.3mL as a 1.6M solution in hexanes, 11.6mmol) was added dropwise over 3 minutes and the reaction stirred for a further 3 minutes. N,N-Dimethylformamide (2.5mL, 31.8mmol) was then added, the reaction stirred for 15 minutes and the cooling bath removed and the reaction stirred for a further 15 minutes before being quenched by water (20mL). The reaction mixture was partitioned between ethyl acetate (250mL) and water (100mL). The organic phase was separated, washed with water (100mL), brine (100mL) then dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by

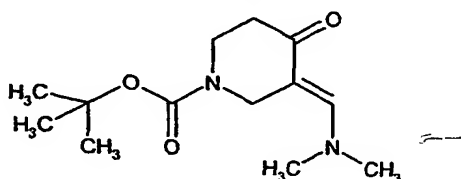
column chromatography on silica gel eluting with a solvent gradient of dichloromethane:methanol (100:0 to 80:20) to give the title compound as an orange semi-solid (1.27g, 48%).

¹H-nmr (CDCl₃, 400MHz) δ: 2.77 (t, 2H), 3.30 (t, 2H), 3.62 (s, 2H), 3.67 (s, 2H), 7.08 (d, 1H), 7.23-7.35 (m, 5H), 8.50 (d, 1H), 10.15 (s, 1H).

LRMS : m/z (ES⁺) 275 [MNa⁺]

Preparation 36

tert-Butyl-3-[(dimethylamino)methylene]-4-oxo-1-piperidinecarboxylate



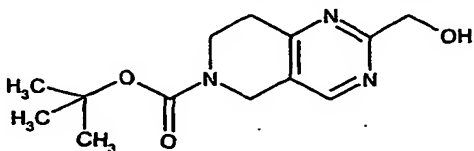
Tert-butyl-4-oxo-1-piperidinecarboxylate (10g, 50mmol) and N,N-dimethylformamide dimethyl acetal (7.3mL, 55mmol) were added to N,N-dimethylformamide (75mL) under nitrogen gas and the mixture heated at 90°C for 8 hours and then stirred for a further 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue partitioned between ethyl acetate (200mL) and brine (200mL). The aqueous phase was re-extracted with ethyl acetate (200mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure to give a brown oil that solidified on standing. Trituration with cyclohexane (20mL) gave the title compound as a light brown solid (8.5g, 67%).

¹H-NMR (400 MHz, CDCl₃) δ: 1.45 (s, 9H), 2.42 (t, 2H), 3.06 (s, 6H), 3.59 (t, 2H), 4.54 (s, 2H), 7.43 (s, 1H).

LRMS : m/z (ES⁺) 277 [MNa⁺].

Preparation 37

tert-Butyl 2-(hydroxymethyl)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate

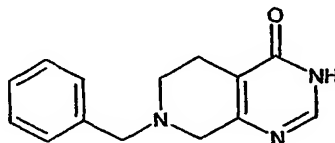


Sodium metal (414mg, 16.5mmol) was added to ethanol (42mL) and stirred at room temperature under nitrogen gas until a clear solution had formed. The compound from preparation 24 (4.2g, 16.5mmol) and 2-hydroxyethanimidamide (J. Am. Chem. Soc.;

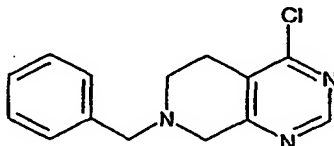
- 68; 1946; 2394) (2g, 18mmol) were added and the reaction mixture heated under reflux for 3 hours and then allowed to cool to room temperature and partitioned between ethyl acetate (100mL) and saturated sodium bicarbonate solution (100mL). The aqueous phase was re-extracted with ethyl acetate (50mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give a brown oil which was purified by column chromatography on silica gel eluting with a solvent gradient of ethyl acetate : methanol (100:0 to 97:03) to give the title compound as a brown oil (3.00g, 73%).
- ^1H -NMR (400MHz, CDCl_3) δ : 1.49 (s, 9H), 2.95 (t, 2H), 3.46 (bs, 1H), 3.75 (t, 2H), 4.59 (s, 2H), 4.77 (d, 2H), 8.44 (s, 1H).

Preparation 38

7-Benzyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4(3H)-one

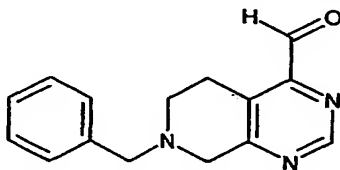


- Sodium metal (10.1g, 0.44mol) was added to ethanol (520mL) and stirred at room temperature under nitrogen gas until a clear solution had formed. Ethyl-3-oxo-N-benzylpiperidine-4-carboxylate hydrochloride (56.5g, 0.19mol) and formamidine acetate (22.9g, 0.22mol) were then added and the reaction mixture heated under reflux for 40 hours. The reaction mixture was concentrated under reduced pressure, and the residue partitioned between water (400mL) and dichloromethane (400mL). The aqueous phase was re-extracted with dichloromethane (2x100mL). The combined organic extracts were dried (MgSO_4) and concentrated under reduced pressure. The resulting solid was triturated with diethyl ether (100mL) and the product collected by filtration to give the title compound as a light brown solid (32.0g, 70%).
- ^1H -nmr (400 MHz, CDCl_3) δ : 2.64 (m, 2H), 2.73 (m, 2H), 3.48 (s, 2H), 3.70 (s, 2H), 7.25-7.34 (m, 5H), 7.97 (s, 1H), 12.37 (bs, 1H).
- LRMS (ES^+): m/z 264 [MNa^+]

Preparation 397-Benzyl-4-chloro-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine

The compound from preparation 38 (11.0g, 42mmol) was mixed with phosphorous
5 oxychloride (80mL) and heated to 90°C under nitrogen gas for 1 hour. The reaction
mixture was concentrated under reduced pressure, re-dissolved in dichloromethane
(100mL) and poured onto ice (100g). The mixture was stirred for 10 minutes, and then
basified with saturated sodium bicarbonate solution. The aqueous phase was extracted
with dichloromethane (3x150mL) and the combined organic extracts were dried
10 (MgSO₄) and concentrated under reduced pressure. The residue was purified by
column chromatography on silica gel eluting with a solvent gradient of
dichloromethane:methanol (100:0 to 90:10) to give the title compound as a brown oil
(9.75g, 90%).

¹H-nmr (400 MHz, CDCl₃) δ: 2.81 (t, 2H), 2.85 (t, 2H), 3.68 (s, 2H), 3.72 (s, 2H), 7.29-
15 7.34 (m, 5H), 8.70 (s, 1H).

Preparation 407-Benzyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-4-carbaldehyde

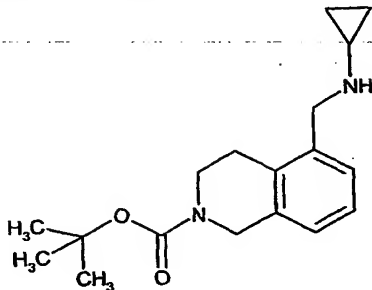
20 Tellurium metal (5.72g, 45mmol) was suspended in tetrahydrofuran (100mL) at room
temperature under nitrogen gas and n-butyl lithium (20mL of a 2.5 M solution in
hexanes, 50 mmol) added over 1 minute. This mixture was stirred for a further 15
minutes and then added to a solution of the compound from preparation 39 (9.75g,
37.5mmol) in tetrahydrofuran (100mL) and the mixture stirred for 15 minutes before
25 being cooled to -78°C. n-Butyl lithium (20mL of a 2.5 M solution in hexanes, 50mmol)
was added over 1 minute and the mixture stirred for 5 minutes before N,N-
dimethylformamide (20mL) was added. The reaction was stirred for a further 30
minutes at -78°C, quenched with water (10mL) then allowed to warm to room
temperature. Ethyl acetate (200mL) and water (100mL) were added, the organic layer

separated and washed with brine (100mL), dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a solvent gradient of dichloromethane:ethyl acetate (100:0 to 50:50) to give the title compound as a brown oil, 3.10g.

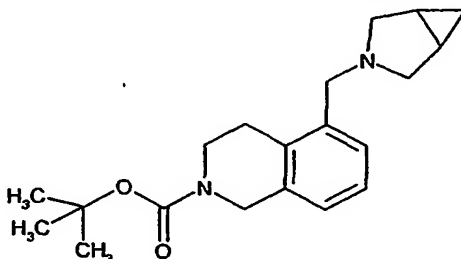
- 5 ¹H-nmr (400MHz, CDCl₃) δ: 2.79 (t, 2H), 3.27 (t, 2H), 3.73 (s, 2H), 3.76 (s, 2H), 7.33 (m, 5H), 9.16 (s, 1H), 10.11 (s, 1H).
LRMS (ES⁺): m/z 276 [MNa⁺]

Preparation 41

- 10 tert-Butyl 5-[(cyclopropylamino)methyl]-3,4-dihydro-2(1H)-isoquinolinecarboxylate



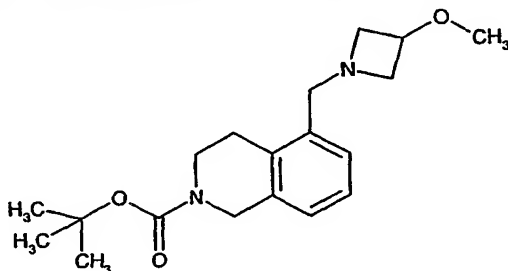
- Cyclopropylamine (0.81mL, 11.4mmol) and acetic acid (0.49μl, 0.85mmol) were added to a solution of the aldehyde from preparation 25 (2.0g, 7.65mmol) in tetrahydrofuran (50mL), and the solution stirred at room temperature for 2 hours. Sodium triacetoxyborohydride (4.0-g, 19.1mmol) was added, and the reaction stirred at room temperature for 72 hours. The mixture was partitioned between 0.88 ammonia (20mL), water (25mL) and ethyl acetate (75mL). The layers were separated, the organic phase washed with brine, dried (MgSO₄) and evaporated under reduced pressure to give the title compound as a clear oil, 2.34g.
- 15 ¹Hnmr (CDCl₃, 400MHz) δ: 0.38 (m, 2H), 0.42 (m, 2H), 1.46 (s, 9H), 2.16 (m, 1H), 2.84 (t, 2H), 3.65 (t, 2H), 3.80 (s, 2H), 4.58 (s, 2H), 7.01 (m, 1H), 7.18 (m, 2H).
LRMS : m/z (ES⁺) 303 [MH⁺], 325 [MNa⁺]
- 20

Preparation 42*tert*-Butyl 5-(3-azabicyclo[3.1.0]hex-3-ylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate

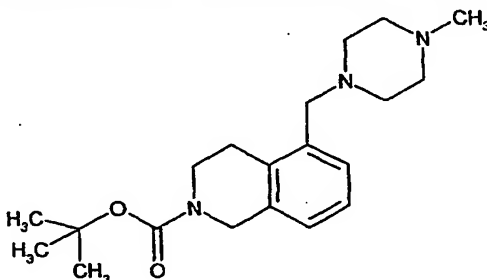
- 5 3-Azabicyclo[3.1.0]hexane hydrochloride (WO 9522547) (203mg, 1.7mmol) sodium acetate (140mg, 1.7mmol), powdered 4Å molecular sieves (500mg) and acetic acid (0.49μl, 0.85mmol) were added to a solution of the aldehyde from preparation 25 (403mg, 1.55mmol) in tetrahydrofuran (10mL), and the solution stirred at room temperature for 1 hour. Sodium triacetoxymethylborohydride (720mg, 3.4mmol) was added, and the reaction stirred at room temperature for 18 hours. The mixture was partitioned between sodium hydroxide solution (60mL, 1N) and ethyl acetate (60mL) and the layers separated. The organic phase was washed with brine (60mL), dried (MgSO₄) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using ethyl acetate: methanol (95:5) as eluant, to give a colourless oil. This was dissolved in diethyl ether (20mL) and the solution extracted with 1N hydrochloric acid (2x20mL). The combined aqueous solutions were then basified to pH 11 using 1N sodium hydroxide solution (50mL), and this aqueous solution extracted with ethyl acetate. These combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure to afford the title compound as a white solid, 224mg.

¹H-nmr (CDCl₃, 400MHz) δ: 0.30 (m, 1H), 0.66 (m, 1H), 1.31 (m, 2H), 1.48 (s, 9H), 2.33 (d, 2H), 2.82 (m, 4H), 3.56 (s, 2H), 3.60 (t, 2H), 4.57 (s, 2H), 6.99 (m, 1H), 7.09 (m, 2H).

LRMS : m/z (ES⁺) 351 [MNa⁺]

Preparation 43*tert*-Butyl 5-[(3-methoxy-1-azetidynyl)methyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate

- Sodium acetate (82mg, 1.0mmol) the aldehyde from preparation 25 (264mg, 1.05mmol) and acetic acid (0.07mL, 1.2mmol) were added to a solution of the amine hydrochloride from preparation 21 (130mg, 1.05mmol) in tetrahydrofuran (10mL), and the solution stirred at room temperature for 0.5 hour. Sodium triacetoxyborohydride (530mg, 2.5mmol) was added, and the reaction stirred at room temperature for 18 hours. The mixture was diluted with ethyl acetate and basified to pH 11 using 0.88 ammonia. The layers were separated, the aqueous phase extracted with ethyl acetate and the combined organic solutions dried (MgSO₄) and evaporated under reduced pressure. The residual yellow oil was purified by column chromatography on silica gel using dichloromethane:methanol (97:3) as eluant to afford the title compound as an oil, 226mg.
- ¹H-nmr (CDCl₃, 400MHz) δ: 1.45 (s, 9H), 2.81 (t, 2H), 2.95 (t, 2H), 3.22 (s, 3H), 3.60 (m, 6H), 4.01 (m, 1H), 4.58 (s, 2H), 7.00 (m, 1H), 7.13 (m, 2H).
- LRMS : m/z (ES⁺) 333.3 [MH⁺]

Preparation 44*tert*-Butyl 5-[(4-methyl-1-piperazinyl)methyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate

- Acetic acid (0.078mL, 1.3mmol) followed by sodium triacetoxyborohydride (572mg, 2.7mmol) were added to a solution of 1-methylpiperazine (0.139mL, 1.25mmol) and the aldehyde from preparation 25 (250mg, 0.96mmol) in tetrahydrofuran (10mL), and the solution stirred at room temperature for 3 hours. The reaction was poured into 2N

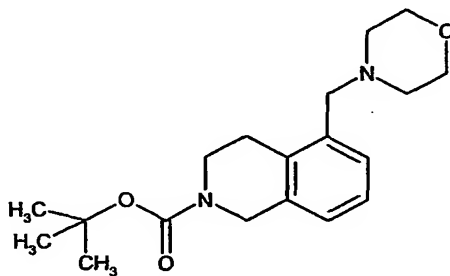
sodium hydroxide solution (50mL), and the mixture extracted with ethyl acetate (3x). The combined organic extracts were washed with brine, dried (MgSO₄) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (95:5:0.5) as eluant to afford the title compound, 201mg.

¹H-nmr (CDCl₃, 400MHz) δ: 1.46 (s, 9H), 1.75 (m, 2H), 2.25 (s, 3H), 2.42 (m, 6H), 2.90 (t, 2H), 3.43 (s, 2H), 3.63 (t, 2H), 4.55 (s, 2H), 7.01 (m, 1H), 7.14 (m, 2H).

LRMS : m/z (ES⁺) 346 [MH⁺]

Preparation 45

tert-Butyl 5-(4-morpholinylmethyl)-3,4-dihydro-2(1H)-isoquinolinecarboxylate

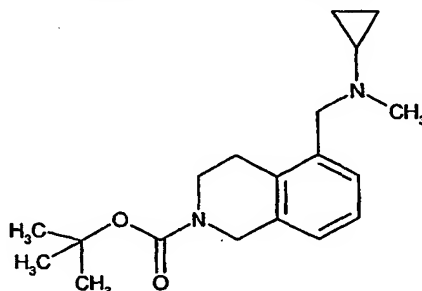


A solution of morpholine (1.34mL, 15.3mmol) and the aldehyde from preparation 25 (2.0g, 7.65mmol) in acetonitrile (40mL) was stirred at room temperature for 1.5 hours, then cooled in an ice-bath. Sodium triacetoxyborohdride (1.95g, 9.18mmol) was added portionwise, the reaction allowed to warm to room temperature and stirred for 6 hours. The reaction was diluted with water (30mL), extracted with ethyl acetate (3x50mL) and the combined organic extracts dried (MgSO₄) and evaporated under reduced pressure to give a yellow oil, 2.60g.

This was purified by column chromatography on silica gel using dichloromethane:diethyl ether (90:10 to 80:20) to afford the title compound as a colourless oil, 2.09g.

¹H-nmr (CDCl₃, 400MHz) δ: 1.47 (s, 9H), 2.39 (m, 4H), 2.90 (m, 2H), 3.40 (s, 2H), 3.62 (m, 6H), 4.57 (s, 2H), 7.00 (m, 1H), 7.10 (m, 2H).

LRMS : m/z (ES⁺) 355 [MNa⁺]

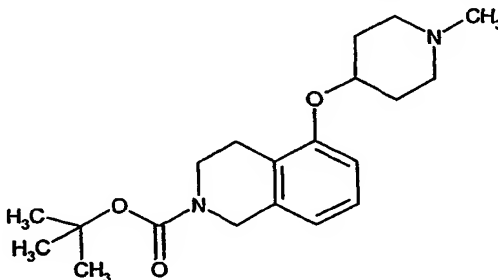
Preparation 46*tert*-Butyl 5-[(cyclopropyl(methyl)amino)methyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate

- 5 A mixture of the amine from preparation 41 (1.1g, 3.43mmol), 37% aqueous formaldehyde (1.05mL, 10.9mmol) and sodium triacetoxyborohydride (3.1g, 14.64mmol) in dichloromethane (50mL) was stirred at room temperature for 18 hours. The reaction mixture was partitioned between 0.88 ammonia (15mL), water (30mL) and dichloromethane (40mL), and the layers separated. The organic phase was washed with brine, dried (MgSO₄) and evaporated under reduced pressure to afford the title compound as a clear oil, 940mg.
- 10

¹H-nmr (CDCl₃, 400MHz) δ: 0.37 (m, 2H), 0.43 (m, 2H), 1.46 (s, 9H), 1.69 (m, 1H), 2.20 (s, 3H), 2.86 (m, 2H), 3.60 (m, 4H), 4.53 (s, 2H), 7.00 (m, 1H), 7.10 (m, 2H).

LRMS : m/z (ES⁺) 317 [MH⁺], 339 [MNa⁺]

15

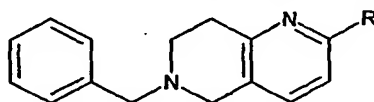
Preparation 47*tert*-Butyl 5-[(1-methyl-4-piperidinyloxy)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate

- A solution of diethylazodicarboxylate (505mg, 2.9mmol) in dichloromethane (3mL) was added dropwise to a cooled (4°C) solution of the tetrahydroisoquinolinol from preparation 22 (498mg, 2mmol) and triphenylphosphine (787mg, 3mmol) in dichloromethane (25mL) and the solution stirred at this temperature for 30 minutes. 1-Methyl-4-hydroxypiperidine (403mg, 3.5mmol) was added and the reaction stirred at room temperature for 17 hours. An additional solution of triphenylphosphine (393mg,
- 20

1.5mmol) and diethylazodicarboxylate (226mg, 1.3mmol) in dichloromethane (2mL), followed by 1-methyl-4-hydroxypiperidine (207mg, 1.8mmol) were added and the reaction stirred for a further 17 hours at room temperature. The mixture was diluted with dichloromethane (50mL), washed with water (2x75mL), dried (MgSO_4) and concentrated under reduced pressure. The residual orange oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (97:3:0.2 to 93:7:0.7) to give the title compound as a yellow oil, 466mg.

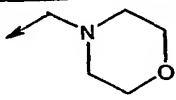
$^1\text{Hnmr}$ (CDCl_3 , 400MHz) δ : 1.48 (s, 9H), 1.86 (m, 2H), 1.97 (m, 2H), 2.29 (s, 3H), 2.32 (m, 2H), 2.61 (m, 2H), 2.77 (t, 2H), 3.63 (t, 2H), 4.34 (m, 1H), 4.54 (s, 2H), 6.69 (d, 2H), 7.09 (dd, 1H). LRMS : m/z (ES^+) 347 [MH^+]

Preparations 48 to 50



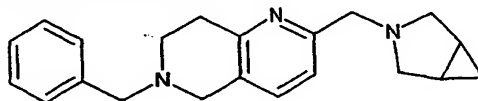
Acetic acid (2.5-3.5eq) followed by the appropriate amine (1.1-1.7eq) were added to a solution of the aldehyde from preparation 29 (1eq) in tetrahydrofuran (5mL per mmol) and the solution stirred for 15 minutes. Sodium triacetoxyborohydride (2-2.3 eq.) was added, and the reaction stirred at room temperature for 17 hours. 2N hydrochloric acid was added, to give a pH of 1, the mixture stirred for 15 minutes, then re-basified to pH 12 using 2N sodium hydroxide solution. The mixture was extracted with dichloromethane, the combined organic extracts dried (MgSO_4) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (95:5:0.5 to 90:10:1) to afford the desired compound.

Prep	R	Yield%	Data
48		76 yellow gum	$^1\text{H-nmr}$ (CDCl_3 , 400MHz) δ : 2.25 (s, 6H), 2.83 (t, 2H), 3.01 (t, 2H), 3.54 (s, 2H), 3.60 (s, 2H), 3.70 (s, 2H), 7.15 (d, 1H), 7.23 (m, 2H), 7.35 (m, 4H). LRMS : m/z (ES^+) 304 [MNa^+]
49		86 yellow oil	$^1\text{H-nmr}$ (CDCl_3 , 400MHz) δ : 1.77 (m, 4H), 2.55 (m, 4H), 2.83 (t, 2H), 3.03 (t, 2H), 3.59 (s, 2H), 3.69 (s, 2H), 3.72 (s, 2H), 7.14-7.38 (m, 7H). LRMS : m/z (ES^+) 308 [MH^+]

Prep	R	Yield%	Data
50		73 yellow oil	$^1\text{H-nmr}$ (CDCl_3 , 400MHz) δ : 2.49 (m, 4H), 2.84 (t, 2H), 3.03 (t, 2H), 3.59 (m, 4H), 3.70 (m, 6H), 7.16-7.38 (m, 7H). LRMS : m/z (ES^+) 346 [MNa^+]

Preparation 51

2-(3-Azabicyclo[3.1.0]hex-3-ylmethyl)-6-benzyl-5,6,7,8-tetrahydro[1,6]naphthyridine

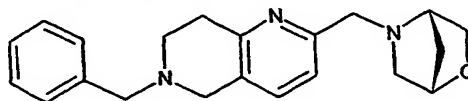


- 5 3-Azabicyclo[3.1.0]hexane hydrochloride (WO 9522547) (300mg, 2.49mmol), sodium acetate (223mg, 2.71mmol) and acetic acid (0.8mL) were added to a solution of the aldehyde from preparation 29 (570mg, 2.26mmol) in tetrahydrofuran (15mL) and dichloromethane (10mL), and the solution stirred at room temperature for 0.5 hour. Sodium triacetoxyborohydride (960mg, 4.52mmol) was added, and the reaction stirred
- 10 at room temperature for 18 hours. The mixture was partitioned between sodium hydroxide solution (60mL, 1N) and ethyl acetate (60mL) and the layers separated. The organic phase was washed with brine (60mL), dried (MgSO_4) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (95:5:0.5) as eluant, to give the title
- 15 compound as a yellow oil, 375mg.
- $^1\text{H-nmr}$ (DMSO-d_6 , 400MHz) δ : 0.30 (m, 1H), 0.62 (m, 1H), 1.35 (m, 2H), 2.35 (m, 2H), 2.76 (m, 2H), 2.88 (m, 4H), 3.52 (s, 2H), 3.57 (s, 2H), 3.64 (s, 2H), 7.03 (d, 1H), 7.30 (m, 6H).
- LRMS : m/z (ES^+) 320 [MH^+]

20

Preparation 52

(1S,4S)-5-[(6-Benzyl-5,6,7,8-tetrahydro[1,6]naphthyridin-2-yl)methyl]-2-oxa-5-azabicyclo[2.2.1]heptane



- 25 A mixture of the aldehyde from preparation 29 (866mg, 3.44mmol), 1S,4S-2-aza-5-oxabicyclo[2.2.1]heptane hydrochloride (700mg, 5.16mmol), sodium acetate (423mg, 5.16mmol) and acetic acid (310mg, 5.16mmol) in tetrahydrofuran (20mL) was stirred at

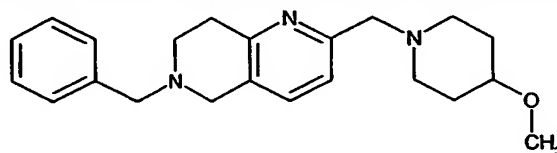
room temperature for 2 hours. 2M Hydrochloric acid (20mL) was added cautiously, the mixture stirred for 10 minutes, then the mixture basified using 1N sodium hydroxide solution. The mixture was extracted with dichloromethane (3x60mL), the combined organic solutions dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 90:10) to afford the title compound as a yellow oil, 783mg.

¹H-nmr (CDCl₃, 400MHz) δ: 1.79 (m, 1H), 1.99 (m, 1H), 2.69 (m, 1H), 2.86 (t, 2H), 2.93 (m, 1H), 3.03 (t, 2H), 3.52 (m, 1H), 3.62 (s, 2H), 3.66 (m, 1H), 3.72 (s, 2H), 3.89 (m, 2H), 4.16 (m, 1H), 4.44 (m, 1H), 7.21-7.83 (m, 7H).

LRMS : m/z (APCI⁺) 336 [MH⁺]

Preparation 53

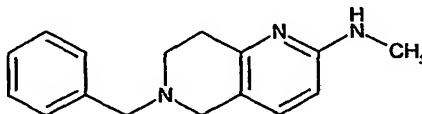
6-Benzyl-2-[(4-methoxy-1-piperidiny)methyl]-5,6,7,8-tetrahydro[1,6]naphthyridine



Triethylamine (0.43mL, 3.2mmol) followed by the aldehyde from preparation 29 (750mg, 3.0mmol) was added to a solution of the piperidine hydrochloride from preparation 94 (483mg, 3.2mmol) in tetrahydrofuran (20mL), and the solution stirred for 1 hour. Sodium triacetoxyborohydride (745mg, 3.5mmol) was added portionwise, and the reaction stirred at room temperature for 18 hours. 2N Hydrochloric acid (4mL) was added, the solution stirred for 5 minutes, then poured into water (80mL), and the pH adjusted to 9 using 2N sodium hydroxide solution. The mixture was extracted with dichloromethane (3x100mL), the combined organic extracts dried (MgSO₄) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (95:5:0.5) to afford the title compound as an oil, that crystallised on standing, 710mg.

¹H-nmr (DMSO-d₆, 400MHz) δ: 1.40 (m, 2H), 1.80 (m, 2H), 2.10 (m, 2H), 2.62 (m, 2H), 2.76 (m, 2H), 2.82 (m, 2H), 3.16 (m, 1H), 3.20 (s, 3H), 3.46 (s, 2H), 3.54 (s, 2H), 3.64 (s, 2H), 7.16 (2xs, 2H), 7.20-7.40 (m, 5H).

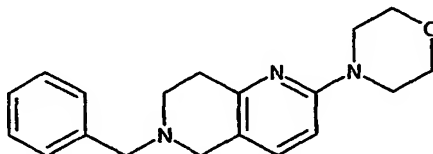
LRMS : m/z (ES⁺) 352 [MH⁺]

Preparation 54*N*-(6-Benzyl-5,6,7,8-tetrahydro[1,6]naphthyridin-2-yl)-*N*-methylamine

Liquid methylamine (20mL) was added to a cooled (-70°C) solution of 6-benzyl-2-chloro-5,6,7,8-tetrahydro[1,6]naphthyridine (WO 9830560) (5.5g, 21.25mmol) in methanol (30mL). The mixture was heated to 140°C in a sealed vessel for 72 hours, then cooled. The reaction mixture was evaporated under reduced pressure and the residual brown oil purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (97:3:0 to 96:4:0.5) to afford the title compound as a white solid, 2.97g

¹H-nmr (CDCl₃, 400MHz) δ: 2.80 (m, 4H), 2.87 (s, 3H), 3.49 (s, 2H), 3.68 (s, 2H), 4.36 (bs, 1H), 6.19 (d, 1H), 7.05 (d, 1H), 7.24 (m, 1H), 7.31 (m, 2H), 7.36 (m, 2H).

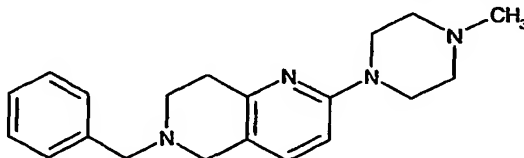
LRMS : m/z (ES⁺) 254 [MH⁺]

Preparation 556-Benzyl-2-(4-morpholinyl)-5,6,7,8-tetrahydro[1,6]naphthyridine

Morpholine (0.33mL, 3.7mmol), sodium *tert*-butoxide (337mg, 3.7mmol), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (124mg, 0.2mmol) and tris(dibenzylideneacetone)dipalladium (0) (92mg, 0.1mmol) were added sequentially to a solution of the bromide from preparation 28 (763mg, 2.5mmol) in toluene (10mL), and the solution purged with nitrogen. The reaction was then stirred at 100°C for 18 hours, cooled and filtered through silica gel, washing through with a solution of dichloromethane:methanol. The filtrate was concentrated under reduced pressure and the residue purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (98:2 to 95:5) to afford the title compound.

¹H-nmr (CDCl₃, 400MHz) δ: 2.79 (m, 2H), 2.81 (m, 2H), 3.41 (m, 4H), 3.46 (s, 2H), 3.67 (s, 2H), 3.78 (m, 4H), 6.41 (d, 1H), 7.12 (s, 1H), 7.30 (m, 5H).

LRMS : m/z (ES⁺) 310 [MH⁺]

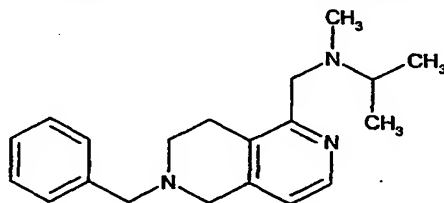
Preparation 566-Benzyl-2-(4-methyl-1-piperazinyl)-5,6,7,8-tetrahydro[1,6]naphthyridine

5 The title compound was obtained in 36% yield, from the bromide from preparation 28 and 1-methylpiperazine, following the procedure described in preparation 55.

¹H-nmr (CDCl₃, 400MHz) δ: 2.30 (s, 3H), 2.49 (m, 4H), 2.79 (m, 2H), 2.82 (m, 2H), 3.49 (m, 6H), 3.08 (s, 2H), 6.42 (d, 1H), 7.09 (d, 1H), 7.35 (m, 5H).

LRMS : m/z (ES⁺) 345 [MNa⁺]

10

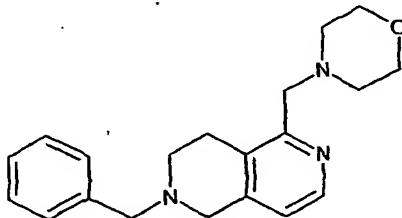
Preparation 57N-[6-Benzyl-5,6,7,8-tetrahydro[2,6]naphthyridin-1-yl)methyl]-N-methyl-2-propanamine

15 N-Isopropyl-N-methylamine (330μl, 3.15mmol) followed by acetic acid (132μl, 2.31mmol) were added to a solution of the aldehyde from preparation 35 (530mg, 2.1mmol) in tetrahydrofuran (15mL), and the solution stirred at room temperature for 1 hour. Sodium triacetoxyborohydride (1.11g, 5.26mmol) was then added, and the reaction stirred for 18 hours. The reaction mixture was partitioned between 1N sodium hydroxide solution (30mL), and ethyl acetate (30mL) and the layers separated. The aqueous phase was extracted with ethyl acetate (30mL) and the combined organic

20 extracts were dried (MgSO₄), and evaporated under reduced pressure to give an oil. This was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (100:0:0 to 90:10:1) to afford the title compound as a yellow oil, 272mg.

25 ¹H-nmr (CDCl₃, 400MHz) δ: 1.06 (d, 6H), 2.13 (s, 3H), 2.77 (t, 2H), 2.85 (m, 1H), 2.99 (t, 2H), 3.58 (s, 2H), 3.62 (s, 2H), 3.66 (s, 2H), 6.78 (m, 1H), 7.35 (m, 5H), 8.23 (m, 1H).

LRMS : m/z (ES⁺) 310 [MH⁺]

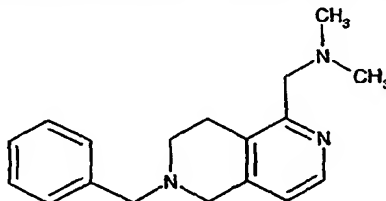
Preparation 582-Benzyl-5-(4-morpholinylmethyl)-1,2,3,4-tetrahydro[2,6]naphthyridine

The title compound was obtained as a yellow oil, from the aldehyde from preparation

35 and morpholine, following a similar procedure to that described in preparation 57.

¹H-nmr (CDCl₃, 400MHz) δ: 2.42 (m, 4H), 2.79 (m, 2H), 2.99 (m, 2H), 3.57-3.78 (m, 10H), 6.80 (d, 1H), 7.20-7.39 (m, 5H), 8.22 (d, 1H).

LRMS m/z (ES⁺) 346 [MNa⁺]

Preparation 59(6-Benzyl-5,6,7,8-tetrahydro[2,6]naphthyridin-1-yl)-N,N-dimethylmethanamine

Dimethylamine (2mL, 2M in tetrahydrofuran, 4mmol) followed by acetic acid (480mg, 8mmol) were added to a solution of the aldehyde from preparation 35 (756mg, 3mmol)

in tetrahydrofuran (15mL), and the solution stirred at room temperature for 10 minutes.

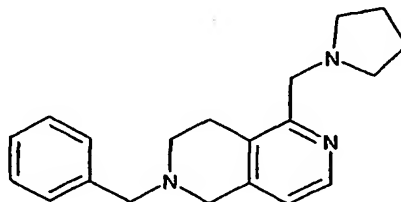
Sodium triacetoxyborohydride (1.27g, 6mmol) was then added, and the reaction stirred for 3 hours. The reaction was quenched by the addition of 2N hydrochloric acid, this

solution stirred for 15 minutes, basified using 1N sodium hydroxide solution, then

extracted with dichloromethane (3x50mL). The combined organic extracts were dried

(MgSO₄), and evaporated under reduced pressure to afford the title compound as an oil, 942mg.

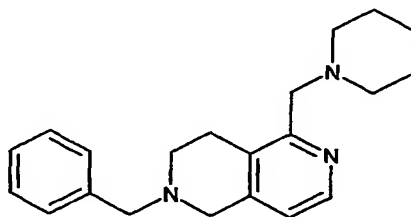
¹H-nmr (CDCl₃, 400MHz) δ: 2.23 (s, 6H), 2.79 (m, 2H), 2.98 (m, 2H), 3.50 (s, 2H), 3.59 (s, 2H), 3.64 (s, 2H), 6.80 (d, 1H), 7.21-7.39 (m, 5H), 8.25 (d, 1H).

Preparation 602-Benzyl-5-(1-pyrrolidinymethyl)-1,2,3,4-tetrahydro[2,6]naphthyridine

The title compound was obtained in 73% yield from the aldehyde from preparation 35 and pyrrolidine, following a similar procedure described in preparation 59, except the reaction was worked up using ethyl acetate and 0.88 ammonia.

^1H -nmr (CDCl_3 , 400MHz) δ : 1.76 (m, 4H), 2.55 (m, 4H), 2.78 (m, 2H), 2.97 (m, 2H), 3.58 (s, 2H), 3.67 (s, 2H), 3.70 (s, 2H), 6.79 (d, 1H), 7.30 (m, 5H), 8.26 (d, 1H).

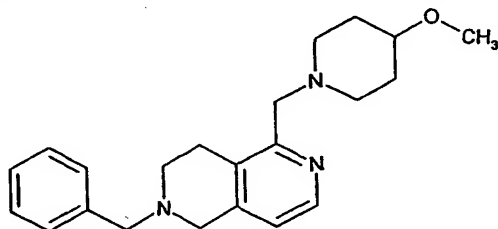
LRMS : m/z (ES^+) 308 [MH^+]

Preparation 612-Benzyl-5-(1-piperidinymethyl)-1,2,3,4-tetrahydro[2,6]naphthyridine

The title compound was obtained in 68% yield from the aldehyde from preparation 35 and piperidine, following a similar procedure to that described in preparation 60.

^1H -nmr (CDCl_3 , 400MHz) δ : 1.40 (m, 2H), 1.50 (m, 4H), 2.40 (m, 4H), 2.77 (m, 2H), 3.00 (m, 2H), 3.52 (s, 2H), 3.59 (s, 2H), 3.67 (s, 2H), 6.79 (d, 2H), 7.25-7.38 (m, 5H), 8.24 (d, 1H).

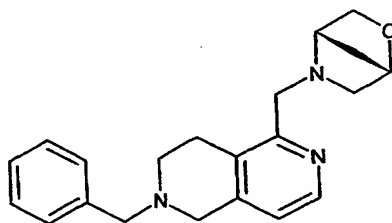
HRMS : m/z (ES^+) 322.2283 [MH^+] $\text{C}_{21}\text{H}_{27}\text{N}_3$ - 322.2278 [MH^+]

Preparation 622-Benzyl-5-[(4-methoxy-1-piperidinyl)methyl]-1,2,3,4-tetrahydro[2,6]naphthyridine

The title compound was obtained as an orange oil from the aldehyde from preparation 35 and 4-methoxypiperidine hydrochloride from preparation 94, following a similar procedure to that described in preparation 60.

¹H-nmr (CDCl₃, 400MHz) δ : 1.58 (m, 2H), 1.85 (m, 2H), 2.22 (m, 2H), 2.77 (m, 4H), 2.99 (m, 2H), 3.19 (m, 1H), 3.32 (s, 3H), 3.60 (m, 4H), 3.69 (s, 2H), 6.80 (d, 1H), 7.20-7.40 (m, 5H), 8.22 (d, 1H).

LRMS : m/z (ES⁺) 352 [MH⁺].

Preparation 63(1S,4S)-5-[(6-benzyl-5,6,7,8-tetrahydro[2,6]naphthyridin-1-yl)methyl]-2-oxa-5-azabicyclo[2.2.1]heptane

15

(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]heptane hydrochloride (344mg, 2.54mmol), followed by sodium acetate (152mg, 1.86mmol) and acetic acid (0.1mL, 1.86mmol) were added to a solution of the aldehyde from preparation 35 (427mg, 1.69mmol) in tetrahydrofuran (15mL), and the solution stirred at room temperature for 1 hour. Sodium triacetoxyborohydride (897mg, 4.23mmol) was added and the reaction stirred at room temperature for 18 hours. The mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate (50mL) and 0.88 ammonia (50mL), the layers separated, and the aqueous phase further extracted with ethyl acetate (50mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (98:2 to 95:5) to afford the title compound as a yellow oil, 324mg.

25

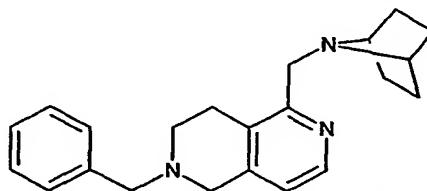
¹H-nmr (CDCl₃, 400MHz) δ: 1.68 (d, 1H), 1.88 (d, 1H), 2.65 (d, 1H), 2.78 (m, 2H), 2.89 (d, 1H), 2.97 (m, 2H), 3.40 (s, 1H), 3.59 (s, 2H), 3.65 (m, 3H), 3.80 (dd, 2H), 4.06 (d, 1H), 4.38 (s, 1H), 6.79 (d, 1H), 7.30 (m, 5H), 8.22 (d, 1H).

LRMS : m/z (ES⁺) 358 [MNa⁺]

5

Preparation 64

5-(7-Azabicyclo[2.2.1]hept-7-ylmethyl)-2-benzyl-1,2,3,4-tetrahydro[2,6]naphthyridine



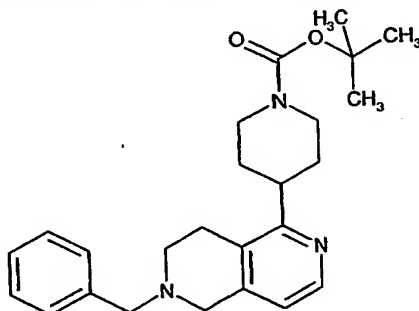
Diisopropylethylamine (720μl, 4.13mmol) was added to a solution of 7-azabicyclo[2.2.1]heptane (Can. J. Chem. 1970; 48(13); 2065) (500mg, 3.75mmol) in dichloromethane (7mL), and the solution stirred for 40 minutes. A solution of the aldehyde from preparation 35 (650mg, 2.57mmol) in dichloromethane (2mL) was added, followed by acetic acid (300μl, 5.16mmol), and the solution stirred for a further 2 hours. Sodium triacetoxyborohydride (1.1g, 5.16mmol) was added, and the reaction stirred at room temperature for 18 hours. The mixture was quenched by the addition of 2N hydrochloric acid (3mL), then basified using 1N sodium hydroxide solution (20mL). The mixture was extracted with dichloromethane (2x), the combined organic extracts dried (Na₂SO₄) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (100:0:0 to 94:5:1) to afford the title compound as a brown oil.

¹H-nmr (CDCl₃, 400MHz) δ: 1.25 (m, 4H), 1.80 (m, 4H), 2.78 (t, 2H), 3.05 (t, 2H), 3.25 (m, 2H), 3.58 (s, 2H), 3.61 (m, 2H), 3.67 (s, 2H), 6.79 (d, 1H), 7.30 (m, 5H), 8.22 (d, 1H).

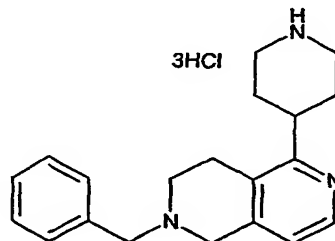
LRMS : m/z (ES⁺) 334 [MH⁺]

Preparation 65

tert-Butyl 4-(6-benzyl-5,6,7,8-tetrahydro[2,6]naphthyridin-1-yl)-1-piperidinecarboxylate



- 5 Zinc (809mg, 12.4mmol) was stirred in 1N hydrochloric acid (5mL) for 5 minutes, the mixture filtered, and the collected zinc washed with water, ethanol and diethyl ether, then dried at 100°C for 5 hours.
- Dibromoethane (28μl, 0.33mmol) was added to a suspension of the zinc in N,N-dimethylformamide (12mL), and the mixture heated at 50°C for 4 minutes, then cooled.
- 10 Trimethylsilyl chloride (54mg, 0.50mmol) was added, the mixture again heated at 50°C for 5 minutes, *tert*-butyl 4-iodo-1-piperidinecarboxylate (EP 1078928) (2.57g, 8.25mmol) added and stirring continued for 5 minutes. A solution of the bromide from preparation 34 (1.0g, 3.3mmol) in N,N-dimethylformamide (2.5mL), tris(dibenzylideneacetone)dipalladium (0) (38mg, 0.07mmol) and tri(o-furyl)phosphine (31mg, 0.13mmol) were added, and the reaction mixture heated at 60°C for 1 hour.
- 15 The cooled mixture was partitioned between dichloromethane (50mL) and water (20mL), and the phases separated. The aqueous layer was extracted with further dichloromethane (2x50mL), and the combined organic extracts were dried (MgSO₄), filtered through Arbocel® and evaporated under reduced pressure. The residual orange oil was purified by column chromatography on silica gel using an elution
- 20 gradient of dichloromethane:methanol (100:0 to 96:4) to give the title compound, as an oil, 1.01g.
- ¹H-nmr (CDCl₃, 400MHz) δ: 1.45 (s, 9H), 1.65 (m, 2H), 1.85 (m, 4H), 2.78 (m, 4H), 2.86 (m, 2H), 3.02 (m, 1H), 3.58 (s, 2H), 3.67 (s, 2H), 6.74 (d, 1H), 7.24-7.37 (m, 5H), 8.25 (d, 1H).
- 25 LRMS : m/z (ES⁺) 408 [MH⁺]

Preparation 662-Benzyl-5-(4-piperidiny)-1,2,3,4-tetrahydro[2,6]naphthyridine trihydrochloride

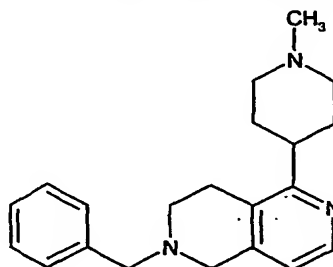
5 A solution of the protected amine from preparation 65 (990mg, 2.43mmol) in dry dichloromethane (30mL) was cooled in an ice/acetone bath and hydrogen chloride gas bubbled through, until saturation. The solution was stirred for a further 2 hours, then evaporated under reduced pressure to afford the title compound as a cream foam, 924mg.

10 ¹H-nmr (CD₃OD, 400MHz) δ: 1.74 (m, 1H), 2.00 (m, 1H), 2.20 (m, 4H), 3.09 (m, 1H), 3.29 (m, 2H), 3.45 (m, 2H), 3.56 (m, 2H), 4.60 (s, 2H), 4.67 (s, 2H), 7.53 (m, 3H), 7.68 (m, 3H), 8.58 (d, 1H).

LRMS : m/z (ES⁺) 308 [MH⁺]

Preparation 67

15 2-Benzyl-5-(1-methyl-4-piperidiny)-1,2,3,4-tetrahydro[2,6]naphthyridine



Triethylamine (675μl, 4.81mmol) was added to a solution of the amine from preparation 66 (914mg, 2.40mmol) in acetonitrile (10mL), followed by dropwise addition of formaldehyde (37% aq., 390mg, 4.81mmol), and the solution stirred at room temperature for 1 hour. Sodium triacetoxyborohydride (2.546g, 12.02mmol) was added portionwise and the reaction stirred at room temperature for 72 hours. The mixture was diluted with water (10mL), then neutralised using sodium bicarbonate solution and extracted with 5% methanol in dichloromethane solution (3x30mL). The combined organic extracts were evaporated under reduced pressure and the residual orange oil, 25 purified by column chromatography on silica gel using an elution gradient of

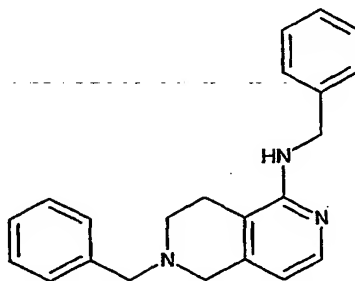
dichloromethane:methanol:0.88 ammonia (96:4:0 to 90:10:0.5) to give the title compound as an orange oil, 690mg.

¹H-nmr (CDCl₃, 400MHz) δ : 1.77 (m, 2H), 2.07 (m, 4H), 2.33 (s, 3H), 2.77 (m, 3H), 2.84 (t, 2H), 3.01 (m, 2H), 3.57 (s, 2H), 3.67 (s, 2H), 6.72 (d, 1H), 7.25-7.35 (m, 5H), 8.27 (d, 1H).

LRMS : m/z (ES⁺) 322 [MH⁺]

Preparation 68

N,6-Dibenzyl-5,6,7,8-tetrahydro[2,6]naphthyridin-1-amine



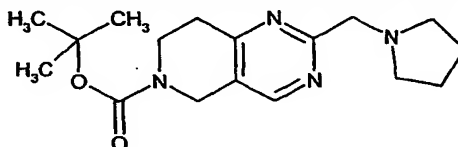
A mixture of the bromide from preparation 34 (303mg, 1mmol) and benzylamine (3mL) was stirred at 160°C for 12 hours. The cooled mixture was poured into ethyl acetate, washed with water, then dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane:ethyl acetate (100:0 to 60:40) to afford the title compound as a pale yellow oil, 249mg.

¹H-nmr (CDCl₃, 400MHz) δ : 2.42 (t, 2H), 2.80 (t, 2H), 3.54 (s, 2H), 3.66 (s, 2H), 4.26 (m, 1H), 4.67 (d, 2H), 6.29 (d, 1H), 7.20-7.40 (m, 10H), 7.94 (d, 1H).

LRMS : m/z (ES⁺) 330 [MH⁺]

Preparation 69

tert-Butyl 2-(1-pyrrolidinylmethyl)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate



Triethylamine (0.36mL, 2.6mmol), followed by methanesulphonyl chloride (0.22mL, 2.9mmol) were added to an ice-cold solution of the alcohol from preparation 37 (600mg, 2.4mmol) in dichloromethane (6mL), and the solution stirred at room temperature for 3 hours. The mixture was evaporated under reduced pressure, and the

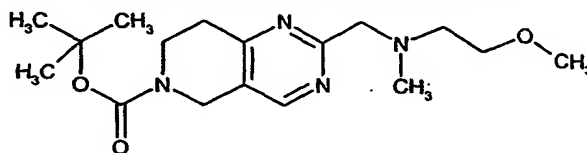
residue re-dissolved in tetrahydrofuran (6mL). Pyrrolidine (0.99mL, 11.9mmol) was added, and the reaction stirred at room temperature for 18 hours. The mixture was partitioned between dichloromethane (50mL) and water (50mL), the layers separated and the organic phase dried (MgSO_4) and evaporated under reduced pressure. The residual yellow oil was purified by column chromatography using an elution gradient of dichloromethane:methanol:0.88 ammonia (98:2:0.2 to 95:5:0.5) to afford the title compound, 600mg.

^1H -nmr (DMSO-d_6 , 400MHz) δ : 1.49 (s, 9H), 1.81 (m, 4H), 2.65 (m, 4H), 2.95 (t, 2H), 3.73 (t, 2H), 3.87 (s, 2H), 4.56 (s, 2H), 8.42 (s, 1H).

LRMS : m/z (ES^+) 319 [MH^+]

Preparation 70

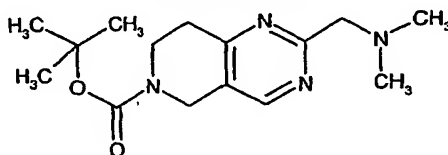
tert-Butyl 2-[[[(2-methoxyethyl)(methyl)amino]methyl]-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate



Diisopropylethylamine (388mg, 3mmol) was added to an ice-cold solution of the alcohol from preparation 37 (530mg, 2mmol) in dichloromethane (10mL). Methanesulphonyl chloride (267mg, 2.33mmol) was added, and the reaction stirred at room temperature for 1 hour. 2-Methoxyethylmethylamine (890mg, 10mmol) was added and the reaction stirred at room temperature for a further 18 hours. The mixture was poured into water, then extracted with dichloromethane (3x40mL), the combined organic extracts dried (MgSO_4) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 97:3) to afford the title compound as a yellow oil, 285mg.

^1H -nmr (CDCl_3 , 400MHz) δ : 1.49 (s, 9H), 2.40 (s, 3H), 2.75 (t, 2H), 2.95 (t, 2H), 3.34 (s, 3H), 3.58 (t, 2H), 3.76 (t, 2H), 3.83 (s, 2H), 4.59 (s, 2H), 8.42 (s, 1H).

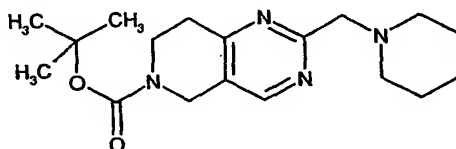
LRMS : m/z (ES^+) 359 [MNa^+]

Preparation 71*tert*-Butyl 2-[(dimethylamino)methyl]-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate

- 5 The title compound was obtained as an orange oil, from the alcohol from preparation 37 and dimethylamine (2M in tetrahydrofuran), using a similar procedure to that described in preparation 70.

¹H-nmr (CDCl₃, 400MHz) δ: 1.49 (s, 9H), 2.38 (s, 6H), 2.98 (t, 2H), 3.66 (s, 2H), 3.74 (t, 2H), 4.58 (s, 2H), 8.44 (s, 1H).

- 10 LRMS : m/z (ES⁺) 315 [MNa⁺]

Preparation 72*tert*-Butyl 2-(1-piperidinylmethyl)-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate

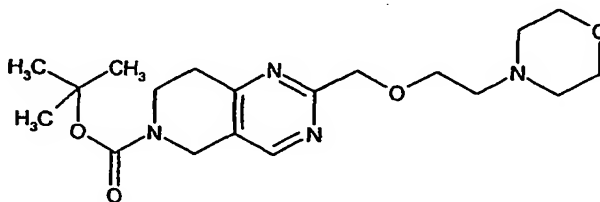
- 15 The title compound was obtained as a yellow oil in 54% yield from the alcohol from preparation 37 and piperidine, using a similar method to that described in preparation 70.

¹H-nmr (CDCl₃, 400MHz) δ: 1.44 (m, 11H), 1.60 (m, 4H), 2.45 (m, 4H), 2.97 (t, 2H), 3.74 (m, 4H), 4.58 (s, 2H), 8.44 (s, 1H).

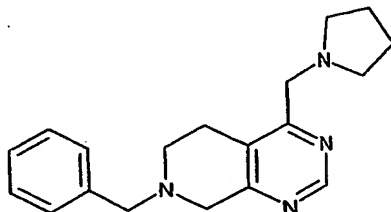
- 20 LRMS : m/z (ES⁺) 355 [MNa⁺]

Preparation 73

tert-Butyl 2-([2-(4-morpholinyl)ethoxy]methyl)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate

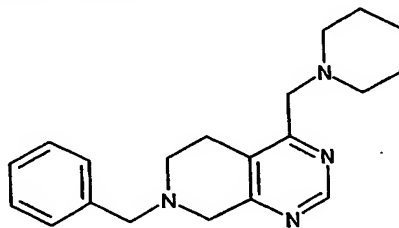


- 5 Triethylamine (305 μ L, 2.19mmol) and methanesulphonyl chloride (185 μ L, 2.39mmol) were added to an ice-cold solution of the alcohol from preparation 37 (500mg, 1.99mmol) in dichloromethane (5mL), and the solution stirred at room temperature for 2 hours.
- 10 4-(2-Hydroxyethyl)morpholine (730 μ L, 5.98mmol) was added dropwise to an ice-cooled suspension of sodium hydride (265mg, 60% dispersion in mineral oil, 6.57mmol) in tetrahydrofuran (5mL), and once addition was complete, the mixture was stirred at room temperature for 1.5 hours.
- 15 The first solution was concentrated under reduced pressure, the residual yellow oil redissolved in tetrahydrofuran (2mL), and the prepared solution of 2-hydroxyethylmorpholine anion, added dropwise. The resulting mixture was stirred at room temperature for 18 hours, then partitioned between water (30mL) and dichloromethane (30mL). The layers were separated, the aqueous phase extracted with further dichloromethane (30mL), and the combined organic solutions dried (Na_2SO_4) and evaporated under reduced pressure. The residual brown oil was purified
- 20 by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (98:2:1) as eluant to afford the title compound as a yellow oil, 600mg.
- ^1H -nmr (CDCl_3 , 400MHz) δ : 1.49 (s, 9H), 2.52 (m, 4H), 2.68 (t, 2H), 2.95 (t, 2H), 3.60 (m, 2H), 3.75 (m, 6H), 4.58 (s, 2H), 4.71 (s, 2H), 8.45 (s, 1H).
- LRMS : m/z (ES^+) 401 [MNa^+]

Preparation 747-Benzyl-4-(1-pyrrolidinylmethyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine

5 Pyrrolidine (322mg, 4.54mmol) and acetic acid (420mg, 7mmol) were added to a solution of the aldehyde from preparation 40 (574mg, 2.27mmol) in tetrahydrofuran (25mL), and the solution stirred at room temperature for 30 minutes. Sodium triacetoxyborohydride (1.48g, 7mmol) was added, and the reaction stirred for a further 4 hours. The mixture was basified using saturated sodium bicarbonate solution, and extracted using dichloromethane (3x50mL). The combined organic extracts were dried
10 (MgSO₄) and evaporated under reduced pressure. The crude product was purified using column chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 85:5) to afford the title compound as a yellow oil, 401mg.

¹H-nmr (CDCl₃, 400MHz) δ: 1.78 (m, 4H), 2.59 (m, 4H), 2.78 (t, 2H), 2.91 (t, 2H), 3.68
15 (s, 2H), 3.69 (s, 2H), 3.71 (s, 2H), 7.25-7.35 (m, 5H), 8.87 (s, 1H).
LRMS : m/z (ES⁺) 309 [MH⁺]

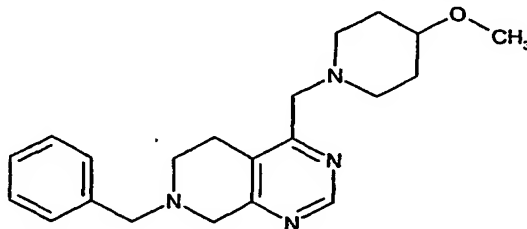
Preparation 757-Benzyl-4-(1-piperidinylmethyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine

20

The title compound was obtained as colourless crystals in 52% yield from the aldehyde from preparation 40 and piperidine, following a similar procedure to that described in preparation 74.

¹H-nmr (CDCl₃, 400MHz) δ: 1.43 (m, 2H), 1.56 (m, 4H), 2.40 (m, 4H), 2.77 (t, 2H), 2.95
25 (t, 2H), 3.49 (s, 2H), 3.68 (s, 2H), 3.71 (s, 2H), 7.35 (m, 5H), 8.86 (s, 1H).

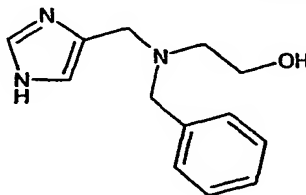
LRMS : m/z (ES⁺) 345 [MNa⁺]

Preparation 767-Benzyl-4-[(4-methoxy-1-piperidinyl)methyl]-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine

The title compound was obtained as a yellow oil in 44% yield, from the aldehyde from preparation 40 and the amine hydrochloride from preparation 94, following a similar procedure to that described in preparation 74, except, 1.2eq of diisopropylethylamine was also used in the reaction.

¹H-nmr (CDCl₃, 400MHz) δ : 1.56 (m, 2H), 1.88 (m, 2H), 2.22 (m, 2H), 2.70 (m, 2H), 2.77 (t, 2H), 2.94 (t, 2H), 3.22 (m, 1H), 3.32 (s, 3H), 3.52 (s, 2H), 3.68 (s, 2H), 3.71 (s, 2H), 7.25-7.36 (m, 5H), 8.86 (s, 1H).

LRMS : m/z (ES⁺) 375 [MNa⁺]

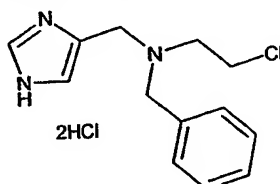
Preparation 772-[Benzyl(1H-imidazol-4-ylmethyl)amino]ethanol

A suspension of 4-imidazolecarboxaldehyde (14g, 145.7mmol) and N-benzylethanolamine (26.4g, 174.8mmol) in tetrahydrofuran (200mL) was stirred at room temperature for 1 hour. Sodium triacetoxyborohydride (37.06g, 174.8mmol) was added portionwise over 40 minutes, and the reaction stirred at room temperature for 18 hours. The reaction was quenched by the addition of water (150mL), the mixture neutralised using saturated sodium bicarbonate solution, and then extracted with dichloromethane (3x300mL). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure to give a yellow oil. This was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (95:5:0 to 90:10:1) to afford the title compound, 18.1g.

¹H-nmr (CDCl₃, 400MHz) δ: 2.73 (t, 2H), 3.63 (t, 2H), 3.67 (s, 2H), 3.71 (s, 2H), 6.88 (s, 1H), 7.25-7.31 (m, 5H), 7.57 (s, 1H). LRMS : m/z (ES⁺) 230 [M-H]⁺

Preparation 78

5 N-Benzyl-N-(2-chloroethyl)-N-(1H-imidazol-4-ylmethyl)amine dihydrochloride



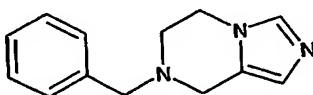
Thionyl chloride (11.35mL, 155.6mmol) was added to a solution of the alcohol from preparation 77 (9.0g, 38.9mmol) in dichloromethane (200mL) over 20 minutes. The solution was then stirred under reflux for 3 hours, and allowed to cool. The mixture was concentrated under reduced pressure and azeotroped with acetonitrile (2x) and dried *in vacuo*, to afford the title compound as a solid, 11.14g.

10 ¹H-nmr (CD₃OD, 400MHz) δ: 3.24 (m, 2H), 3.78 (m, 2H), 4.15 (s, 2H), 4.25 (s, 2H), 7.40 (m, 3H), 7.46 (m, 2H), 7.64 (s, 1H), 8.88 (s, 1H). LRMS : m/z (ES⁺) 250 [MH]⁺

Preparation 79

15

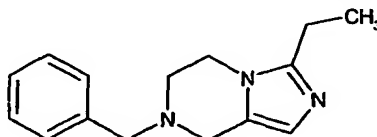
7-Benzyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine



Triethylamine (19.55mL, 140mmol) was added to a solution of the chloride from preparation 78 (11.12g, 38.9mmol) in acetonitrile (150mL) over 20 minutes, and the reaction heated under reflux for 6 hours. The cooled mixture was filtered, and the filtrate concentrated under reduced pressure. The residual oil was partitioned between dichloromethane (300mL) and saturated sodium bicarbonate solution (150mL) and the phases separated. The aqueous layer was extracted with further dichloromethane (2x300mL), and the combined organic extracts dried (MgSO₄) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 95:5) to afford the title compound as an orange solid, 3.62g.

25 ¹H-nmr (CDCl₃, 400MHz) δ: 2.84 (t, 2H), 3.67 (s, 2H), 3.70 (s, 2H) 4.02 (t, 2H), 6.73 (s, 1H), 7.25-7.35 (m, 6H). LRMS : m/z (ES⁺) 214 [MH]⁺

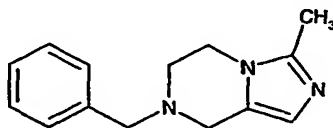
30

Preparation 807-Benzyl-3-ethyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine

n-Butyllithium (3.3mL, 1.6M in hexanes, 5.28mmol) was added dropwise to a cooled (-78°C) solution of the compound from preparation 79 (1.0g, 4.69mmol) in tetrahydrofuran (10mL), so as to maintain the temperature below -70°C, and the solution then allowed to warm to 0°C over 30 minutes. Ethyl iodide (1.22mL, 15.0mmol) was added, and the mixture stirred at 0°C for 45 minutes. The reaction was allowed to warm to room temperature, then partitioned between ethyl acetate (30mL) and saturated sodium bicarbonate solution (6mL). The phases were separated, the aqueous layer extracted with further ethyl acetate, and the combined organic extracts dried (MgSO₄) and evaporated under reduced pressure. The residual orange oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (99:1 to 90:10) to afford the title compound as an orange oil, 552mg.

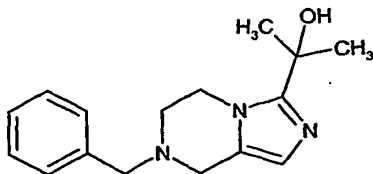
¹H-nmr (CDCl₃, 400MHz) δ: 1.30 (t, 3H), 2.62 (q, 2H), 2.84 (t, 2H), 3.63 (s, 2H), 3.68 (s, 2H), 3.85 (t, 2H), 6.62 (s, 1H), 7.24-7.34 (m, 5H).

LRMS : m/z (ES⁺) 242 [MH⁺]

Preparation 817-Benzyl-3-methyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine

The title compound was obtained as an orange oil in 89% yield from the compound from preparation 79 and methyl iodide, following the procedure described in preparation 80.

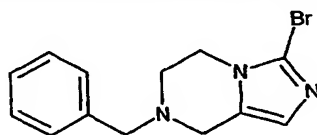
¹H-nmr (CDCl₃, 400MHz) δ: 2.30 (s, 3H), 2.84 (t, 2H), 3.62 (s, 2H), 3.68 (s, 2H), 3.83 (t, 2H), 6.59 (s, 1H), 7.25-7.34 (m, 5H). LRMS : m/z (ES⁺) 228 [MH⁺].

Preparation 822-(7-Benzyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazin-3-yl)-2-propanol

n-Butyllithium (6.21mL, 1.6M in hexanes, 9.94mmol) was added dropwise to a cooled (-78°C) solution of the compound from preparation 79 (2.0g, 9.38mmol) in tetrahydrofuran (20mL), so as to maintain the temperature below -70°C, and the solution then allowed to warm to 0°C over 30 minutes. Acetone (2.06mL, 28.13mmol) was added, and the mixture stirred at 0°C for 45 minutes. The reaction was allowed to warm to room temperature, then quenched by the addition of water (10mL), then neutralised using 2N hydrochloric acid. The mixture was extracted with ethyl acetate (3x50mL), and the combined organic extracts dried (MgSO₄) and evaporated under reduced pressure. The residual orange oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (99:1 to 94:6) to afford the title compound as a solid, 1.21g.

¹H-nmr (CDCl₃, 400MHz) δ: 1.63 (s, 6H), 2.80 (t, 2H), 3.63 (s, 2H), 3.67 (s, 2H), 4.23 (t, 2H), 6.60 (s, 1H), 7.25-7.39 (m, 5H).

LRMS : m/z (ES⁺) 272 [MH⁺]

Preparation 837-Benzyl-3-bromo-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine

n-Butyllithium (2.2mL, 2.5M in hexane, 5.5mmol) was added dropwise to a cooled (-78°C) solution of the compound from preparation 79 (1.07g, 5mmol) in tetrahydrofuran (20mL), and the solution stirred for 15 minutes. Bromine (880mg, 5.5mmol) was then added dropwise, the reaction stirred for a further 15 minutes, then poured into water. The mixture was extracted with dichloromethane (3x50mL), the combined organic extracts dried (MgSO₄) and concentrated under reduced pressure. The crude product was purified by column chromatography using an elution gradient of dichloromethane:methanol (100:0 to 95:5), then repeated using dichloromethane:ethyl

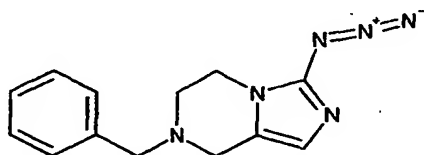
acetate (100:0 to 60:40), to afford the title compound as a pale yellow crystalline solid, 979mg.

¹H-nmr (CDCl₃, 400MHz) δ: 2.86 (t, 2H), 3.62 (s, 2H), 3.69 (s, 2H), 3.86 (t, 2H), 6.71 (s, 1H), 7.25-7.34 (m, 5H). LRMS : m/z (ES⁺) 314, 316 [MNa⁺]

5

Preparation 84

3-Azido-7-benzyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine



n-Butyllithium (1.23mL, 2.5M in hexanes, 3.09mmol) was added to a cooled (-78°C) solution of the compound from preparation 79 (548mg, 2.57mmol) in tetrahydrofuran (10mL), and the mixture stirred for 10 minutes. p-Toluenesulphonyl azide (WO 9824759) (609mg, 3.09mmol) was added, the reaction stirred for a further 10 minutes, and then saturated sodium bicarbonate solution (4mL) added. The mixture was warmed to room temperature, diluted with brine, and extracted with dichloromethane (2x60mL). The combined organic solutions were dried (MgSO₄), and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane:ethyl acetate (100:0 to 60:40) to afford the title compound as a yellow-orange oil, 154mg.

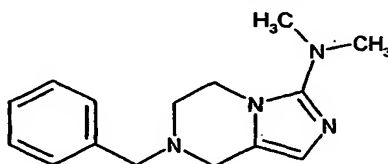
¹H-nmr (CDCl₃, 400MHz) δ: 2.79 (t, 2H), 3.58 (s, 2H), 3.66 (s, 2H), 3.70 (t, 2H), 6.56 (s, 1H), 7.25-7.36 (m, 5H).

20

LRMS : m/z (ES⁺) 277 [MNa⁺]

Preparation 85

N-(7-Benzyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazin-3-yl)-N,N-dimethylamine



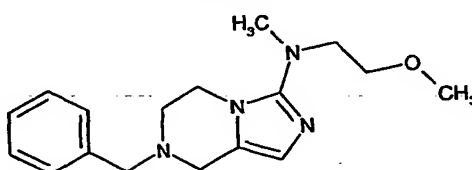
25

A solution of the bromide from preparation 83 (950mg, 3.25mmol) in ethanolic dimethylamine (33%, 12mL) was heated at 140°C in a sealed vessel for 4 days. The cooled mixture was poured into water, and extracted with dichloromethane (3x50mL). The combined organic extracts were dried (MgSO₄) and evaporated under reduced

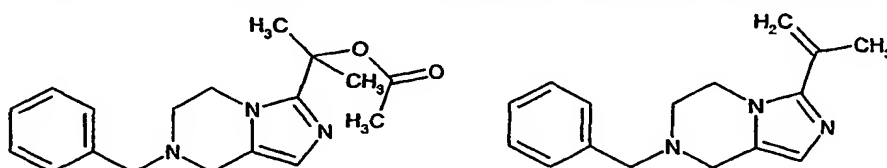
pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol (100:0 to 95:5) and repeated using ethyl acetate:methanol (100:0 to 95:5) to afford the title compound as an orange oil, 172mg. ¹H-nmr (CDCl₃, 400MHz) δ: 2.75 (s, 6H), 2.79 (t, 2H), 3.60 (s, 2H), 3.67 (s, 2H), 3.80 (t, 2H), 6.44 (s, 1H), 7.25-7.38 (m, H). LRMS : m/z (ES⁺) 257 [MH⁺]

Preparation 86

7-Benzyl-N-(2-methoxyethyl)-N-methyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazin-3-amine



A solution of the bromide from preparation 83 (52mg, 0.18mmol) in N-(2-methoxyethyl)methylamine (3mL) was heated at 140°C for 18 hours in a sealed vessel. The reaction was heated to 185°C for a further 5 hours, then cooled and partitioned between 0.1N sodium hydroxide solution and dichloromethane. The layers were separated, the aqueous phase extracted with further dichloromethane (2x50mL), and the combined organic solutions dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate:methanol:0.88 ammonia (100:0:0 to 93:7:0.7) to afford the title compound as a yellow oil, 75mg. ¹H-nmr (CDCl₃, 400MHz) δ: 2.76 (m, 5H), 3.18 (t, 2H), 3.32 (s, 3H), 3.48 (t, 2H), 3.59 (s, 2H), 3.66 (s, 2H), 3.82 (t, 2H), 6.46 (s, 1H), 7.25-7.36 (m, 5H). LRMS : m/z (ES⁺) 323 [MNa⁺]

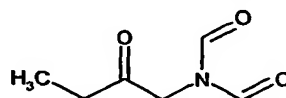
Preparation 871-(7-Benzyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazin-3-yl)-1-methylethyl acetate
andPreparation 885 7-Benzyl-3-isopropenyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine

Acetic anhydride (541 μ l, 5.74mmol) was added dropwise to a solution of the alcohol from preparation 82 (1.25g, 4.59mmol) in pyridine (20mL), containing 4-dimethylaminopyridine (70mg, 0.57mmol). The solution was stirred at room temperature for 72 hours then evaporated under reduced pressure. The residual orange oil was partitioned between ethyl acetate (100mL) and 10% sodium bicarbonate solution (50mL), and the layers separated. The organic phase was washed with water (2x50mL), dried (MgSO₄) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 94:6) to afford the title compound as an orange oil, 471mg.

¹H-nmr (CDCl₃, 400MHz) (2:3 mixture of compounds) δ : 1.84 (s, 6H), 2.02 (s, 3H), 2.19 (s, 3H), 2.80 (t, 2H), 2.80 (t, 2H), 3.65 (2xs, 4H), 3.70 (2xs, 4H), 4.04 (m, 2H), 4.04 (m, 2H), 5.29 (s, 2H), 6.64 (s, 1H), 6.77 (s, 1H), 7.27-7.37 (m, 5H), 7.27-7.37 (m, 5H).

20 LRMS : m/z (ES⁺) 336 [MNa⁺] (preparation 87)

LRMS : m/z (ES⁺) 254 [MH⁺] (preparation 88)

Preparation 89Formyl(2-oxobutyl)formamide

25

A mixture of bromobutan-2-one (10g, 66mmol), and sodium diformylamide (6.8g, 72mmol) in acetonitrile (50mL) was stirred at room temperature for 3 hours, then warmed to 35°C for 2 hours. The mixture was stirred for a further 48 hours at room temperature, then filtered, washing through with additional acetonitrile (50mL). The

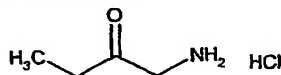
filtrate was evaporated under reduced pressure to afford the title compound as a clear oil, 9.1g.

$^1\text{H-nmr}$ (CDCl_3 , 400MHz) δ : 1.10 (t, 3H), 2.50 (q, 2H), 4.42 (s, 2H), 8.90 (bs, 2H).

5

Preparation 90

1-Amino-2-butanone hydrochloride



10

A solution of the compound from preparation 89 (9.1g, 63.6mmol) in ethanolic hydrochloric acid (5%, 175mL) was stirred at room temperature for 48 hours. The reaction was then evaporated under reduced pressure to afford the title compound as a tan-coloured solid, 6.3g.

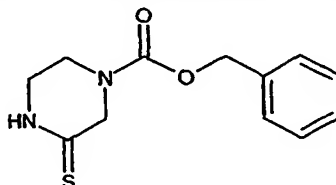
$^1\text{H-nmr}$ (DMSO-d_6 , 400MHz) δ : 1.96 (t, 3H), 2.50 (q, 2H), 3.84 (bs, 2H), 8.38 (bs, 3H).

LRMS : m/z (ES^+) 175 [$2\text{M}+\text{H}$] $^+$

15

Preparation 91

Benzyl 3-thioxo-1-piperazinecarboxylate



20

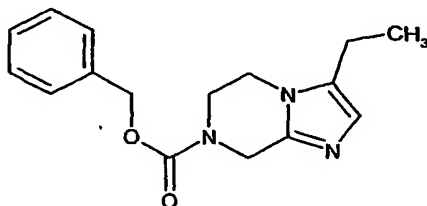
Lawesson's reagent (10.1g, 20mmol) was added to a solution of benzyl 3-oxo-1-piperazinecarboxylate (10g, 43mmol) in tetrahydrofuran (110mL), and the reaction heated under reflux for 4 hours. The cooled mixture was concentrated under reduced pressure and the residue partitioned between 1N sodium hydroxide solution (150mL) and ethyl acetate (250mL), and the layers separated. The organic extract was washed with 1N sodium hydroxide solution (2x100mL), then brine (100mL), and the combined aqueous solutions extracted with ethyl acetate (200mL). The combined organic solutions were dried (MgSO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using dichloromethane:methanol (98:2) as eluant to afford the title compound as a tan-coloured solid, 6.7g.

25

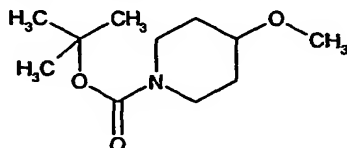
$^1\text{H-nmr}$ (DMSO-d_6 , 400MHz) δ : 3.24-3.34 (m, 2H), 3.58 (m, 2H), 4.36 (s, 2H), 5.10 (s,

30

2H), 7.30-7.40 (m, 5H). LRMS : m/z (ES^+) 273 [MNa^+]

Preparation 92Benzyl 3-ethyl-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate

- 5 Methyl iodide (2.18mL, 35mmol) was added to a solution of the compound from preparation 91 (1g, 3.5mmol) in tetrahydrofuran (15mL), and the reaction stirred at room temperature for 18 hours. The mixture was concentrated under reduced pressure, the residue re-dissolved in tetrahydrofuran (15mL), diisopropylethylamine (1mL) and the compound from preparation 90 (500mg, 4mmol) added, and the solution stirred at room temperature for 18 hours, followed by a further 2 hours under reflux.
- 10 Acetic acid (15mL) was added, the mixture concentrated under reduced pressure to a volume of about 15mL, then heated under reflux for 1 hour. The reaction was evaporated under reduced pressure and the residue purified by column chromatography on silica gel using dichloromethane:methanol (95:5) as eluant to afford the title compound as a pale orange solid, 620mg.
- 15 ¹H-nmr (DMSO_d₆, 400MHz) δ: 1.14 (t, 3H), 3.10 (q, 2H), 3.60 (m, 2H), 3.82 (m, 2H), 4.60 (bs, 2H), 5.12 (s, 2H), 6.64 (s, 1H), 7.36 (m, 5H).
LRMS : m/z (ES⁺) 286 [MH]⁺

Preparation 93*tert*-Butyl 4-methoxy-1-piperidinecarboxylate

- 20 Sodium hydride (1.19g, 60% in mineral oil, 29.7mmol) was added portionwise to a cooled (10°C) solution of *tert*-butyl 4-hydroxy-1-piperidinecarboxylate (Bioorg. Med. Chem. Lett. 10;24;2000;2815) in tetrahydrofuran (80mL), and the suspension stirred at room temperature for 1 hour. Iodomethane (1.85mL, 29.7mmol) was added, and the reaction stirred at 50°C for 20 hours. The mixture was diluted with water (50mL), extracted with ethyl acetate (2x150mL) and the combined organic extracts washed with saturated sodium bicarbonate solution (50mL), dried (MgSO₄) and evaporated under reduced pressure, to afford the title compound as a golden oil, 5.24g.
- 25

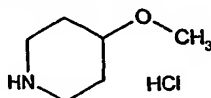
¹H-nmr (CDCl₃, 400MHz) δ: 1.47 (s, 9H), 1.50 (m, 2H), 1.80 (m, 2H), 3.08 (m, 2H), 3.34 (m, 4H), 3.75 (m, 2H).

LRMS : m/z (ES⁺) 238 [MNa⁺]

5

Preparation 94

4-Methoxypiperidine hydrochloride



Hydrogen chloride was bubbled through an ice-cooled solution of the compound from preparation 93 (5.2g, 24.2mmol) in dichloromethane (100mL), and the reaction stirred for 1.5 hours. The solution was purged with nitrogen, then evaporated under reduced pressure to afford the title compound as an off-white solid, 3.67g.

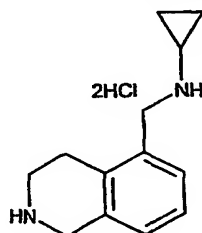
¹H-nmr (DMSO-d₆, 400MHz) δ: 1.87 (m, 2H), 1.99 (m, 2H), 3.10 (m, 2H), 3.28 (m, 2H), 3.36 (s, 3H), 3.54 (m, 1H).

LRMS : m/z (ES⁺) 231 [2MH⁺]

15

Preparation 95

N-(1,2,3,4-Tetrahydro-5-isoquinolylmethyl)cyclopropanamine dihydrochloride



Hydrogen chloride was bubbled through an ice-cooled solution of the protected amine from preparation 29 (1.17g, 3.87mmol) in dichloromethane (35mL), for 20 minutes. The reaction was then stirred for a further 30 minutes at room temperature and evaporated under reduced pressure to afford the title compound as a white solid, 1.15g.

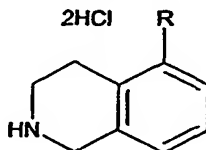
¹Hnmr (DMSO-d₆, 400MHz) δ: 0.83 (m, 2H), 0.95 (m, 2H), 2.67 (m, 1H), 3.10 (t, 2H), 3.34 (m, 2H), 4.17 (s, 2H), 4.26 (s, 2H), 7.26 (m, 2H), 7.48 (d, 1H), 9.60 (bs, 4H).

LRMS : m/z (ES⁺) 203 [MH⁺]

25

Preparations 96 to 99

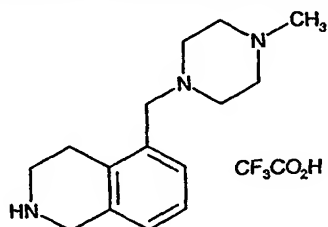
The following compounds of general structure:



5 were prepared from the corresponding protected amines, following the procedure described in preparation 95:

Prep no	R	Form	Data
96		White solid	¹ Hnmr (DMSOd ₆ , 400MHz) (rotamers) δ: 0.70 (m, 4H), 1.15 (m, 1H), 2.67 (2xs, 3H), 2.90 (m, 1H), 3.33 (m, 2H), 4.20 (s, 2H), 4.40 (2xs, 2H), 7.30 (m, 2H), 7.60 (m, 1H), 9.63 (bs, 2H), 10.76 (bs, 1H). LRMS : m/z (ES ⁺) 217 [MH ⁺]
97		White foam	¹ Hnmr (DMSOd ₆ , 400MHz) δ: 0.59 (m, 1H), 1.34 (m, 1H), 1.72 (m, 2H), 3.18 (m, 2H), 3.36 (m, 6H), 4.21 (s, 2H), 4.34 (d, 2H), 7.24 (m, 2H), 7.73 (m, 1H), 9.58 (bs, 2H), 10.95 (bs, 1H). LRMS : m/z (ES ⁺) 229 [MH ⁺]
98		White foam	¹ Hnmr (DMSOd ₆ , 400MHz) δ: 3.01-3.40 (m, 7H), 3.90 (bs, 1H), 4.01 (bs, 1H), 4.22 (m, 6H), 4.40 (s, 2H), 7.28 (m, 2H), 7.43 (m, 1H), 9.40-9.56 (m, 2H). LRMS : m/z (ES ⁺) 234 [MH ⁺]
99		White solid	¹ Hnmr (DMSOd ₆ , 400MHz) δ: 3.20 (m, 4H), 3.37 (m, 2H), 3.62 (m, 2H), 3.90 (m, 4H), 4.22 (m, 2H), 4.32 (s, 2H), 7.30 (m, 2H), 7.62 (m, 1H), 9.58 (bs, 2H), 11.40 (bs, 1H). LRMS : m/z (ES ⁺) 233 [MH ⁺]

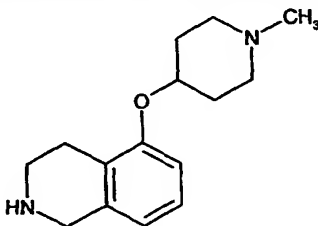
(a)-isolated as the trihydrochloride salt

Preparation 1005-[(4-Methyl-1-piperazinyl)methyl]-1,2,3,4-tetrahydroisoquinoline trifluoroacetate

Trifluoroacetic acid (1mL) was added to an ice-cooled solution of the protected amine from preparation 44 (200mg, 0.58mmol) in dichloromethane (3mL), and the reaction stirred at room temperature for 3 hours. The mixture was concentrated under reduced pressure and the residue azeotroped with toluene (2x) and dichloromethane (3x) to afford the title compound.

¹Hnmr (DMSOd₆, 400MHz) δ : 2.79 (s, 3H), 2.81-3.04 (m, 6H), 3.38 (m, 4H), 3.58 (m, 2H), 4.28 (t, 2H), 7.16 (m, 1H), 7.24 (m, 2H), 9.03 (bs, 2H).

LRMS : m/z (ES⁺) 246 [MH⁺]

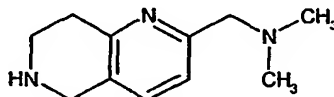
Preparation 1015-[(1-Methyl-4-piperidinyl)oxy]-1,2,3,4-tetrahydroisoquinoline

15

Trifluoroacetic acid (5mL) was added dropwise to a solution of the protected amine from preparation 47 (420mg, 1.21mmol) in dichloromethane (5mL), and the solution stirred at room temperature for 4 hours. The solution was concentrated under reduced pressure and azeotroped twice with toluene. The residual oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (97:3:0.2 to 90:10:1) to afford the title compound as a colourless oil, 198mg.

¹Hnmr (CDCl₃, 400MHz) δ : 1.73 (m, 1H), 1.87 (m, 2H), 1.98 (m, 2H), 2.30 (s, 3H), 2.33 (m, 2H), 2.62 (m, 2H), 2.68 (t, 2H), 3.13 (t, 2H), 3.97 (s, 2H), 4.35 (m, 1H), 6.61 (d, 1H), 6.66 (d, 1H), 7.07 (dd, 1H).

LRMS : m/z (ES⁺) 247 [MH⁺].

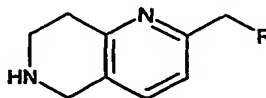
Preparation 102*N,N*-Dimethyl(5,6,7,8-tetrahydro[1,6]naphthyridin-2-yl)methanamine

A solution of the protected naphthyridine from preparation 48 (600mg, 2.13mmol) in methanol (60mL) was purged with argon, then heated to reflux. Immediately this was achieved, 10% palladium on charcoal (600mg) and ammonium formate (268mg, 4.26mmol) were added, and the mixture stirred under reflux for 3 minutes. The reaction vessel was then immersed in cold water, and the cooled mixture then filtered through Arbocel®, washing through with ethanol. The filtrate was evaporated under reduced pressure and the residual oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (97:3:0.2 to 90:10:1) to afford the title compound as a colourless oil, 259mg.

¹H-nmr (CDCl₃, 400MHz) δ: 2.28 (s, 6H), 2.96 (t, 2H), 3.21 (t, 2H), 3.56 (s, 2H), 3.98 (s, 2H), 7.18 (d, 1H), 7.25 (d, 1H). LRMS : m/z (ES⁺) 214 [MNa⁺].

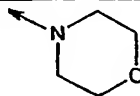
Preparations 103 to 106

The following compounds of general structure:



were prepared from the corresponding protected naphthyridines, following a similar procedure to that described in preparation 102.

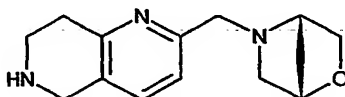
Prep. No.	R	Yield%/Form	Data
103		55 colourless oil	¹ H-nmr (CDCl ₃ , 400MHz) δ: 1.78 (m, 4H), 2.58 (m, 4H), 2.94 (t, 2H), 3.21 (t, 2H), 3.73 (s, 2H), 3.98 (s, 2H), 7.17 (d, 1H), 7.25 (d, 1H). LRMS : m/z (ES ⁺) 218 [MH ⁺]
105		88 colourless oil	¹ H-nmr (DMSO-d ₆ , 400MHz) δ: 1.40 (m, 2H), 1.80 (m, 2H), 2.16 (m, 2H), 2.64 (m, 2H), 2.70 (m, 2H), 2.98 (m, 2H), 3.18 (s, 3H), 3.20 (m, 1H), 3.44 (s, 2H), 3.80 (s, 2H), 7.12 (d, 1H), 7.38 (d, 1H). LRMS : m/z (ES ⁺) 262 [MH ⁺]

Prep. No.	R	Yield% /Form	Data
106		72 yellow oil	$^1\text{H-nmr}$ (CDCl_3 , 400MHz) δ : 2.55 (m, 4H), 2.93 (t, 2H), 3.21 (t, 2H), 3.60 (s, 2H), 3.71 (m, 4H), 3.98 (s, 2H), 7.19 (d, 1H), 7.26 (d, 1H). LRMS : m/z (ES^+) 234 [MH^+]

(a)-compound isolated without column chromatography

Preparation 107

(1S,4S)-5-(5,6,7,8-Tetrahydro[1,6]naphthyridin-2-ylmethyl)-2-oxa-5-azabicyclo[2.2.1]heptane

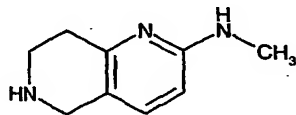


1-Chloroethyl chloroformate (79mg, 0.55mmol) was added to a solution of the compound from preparation 52 (168mg, 0.5mmol) in acetonitrile (5mL), and the reaction warmed to 50°C, and the stirred for 30 minutes. The cooled mixture was concentrated under reduced pressure and the residue re-dissolved in methanol (5mL), and the solution stirred under reflux for 45 minutes. The cooled solution was purified directly by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (93:7:1) to afford the title compound as a pale orange oil, 66mg.

$^1\text{H-nmr}$ (CDCl_3 , 400MHz) δ : 1.80 (m, 1H), 1.99 (m, 1H), 2.71 (m, 1H), 3.01 (m, 1H), 3.04 (t, 2H), 3.32 (t, 2H), 3.59 (m, 1H), 3.67 (m, 1H), 3.94 (q, 2H), 4.11 (s, 2H), 4.16 (m, 1H), 4.44 (m, 1H), 7.35 (s, 2H); LRMS : m/z (APCI^+) 246 [MH^+]

Preparation 108

N-Methyl-5,6,7,8-tetrahydro[1,6]naphthyridin-2-amine



A mixture of the protected naphthyridine from preparation 54 (1.28g, 5.05mmol) and 10% palladium on charcoal (130mg) in 1N hydrochloric acid (10.5mL) was hydrogenated at 30°C and 30 psi for 17 hours. The reaction mixture was filtered through Arbocel®, washing through with water and ethanol. The combined filtrate was evaporated under reduced pressure and the residual solid was suspended in a warm solution of water (20mL) and 1N hydrochloric acid (4mL) and the mixture filtered

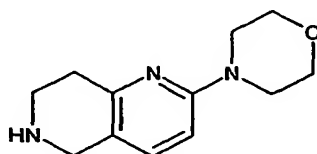
through Arbocel®. The filtrate was concentrated under reduced pressure and azeotroped with ethanol, ethyl acetate and diethyl ether. The product was recrystallised from methanol and ethyl acetate to afford the title compound as a solid, 300mg.

¹H-nmr (D₂O, 400MHz) δ: 2.95 (s, 3H), 3.15 (m, 2H), 3.57 (m, 2H), 4.20 (s, 2H), 6.84 (d, 1H), 7.59 (d, 1H).

LRMS : m/z (ES⁺) 164 [MH⁺]

Preparation 109

2-(4-Morpholinyl)-5,6,7,8-tetrahydro[1,6]naphthyridine



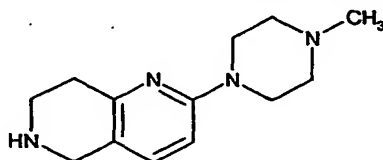
Ammonium formate (1.02g, 16mmol), followed by 10% palladium on charcoal (1g) were added to a solution of the protected naphthyridine from preparation 55 (1g, 3.2mmol) in methanol (20mL), and the reaction heated under reflux for 1.5 hours. The cooled mixture was filtered through Arbocel®, washing through with dichloromethane and methanol, and the filtrate evaporated under reduced pressure. The product was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (98:2:0 to 94:5:1) to afford the title compound, 425mg.

¹H-nmr (CDCl₃, 400MHz) δ: 2.79 (t, 2H), 3.17 (t, 2H), 3.44 (m, 4H), 3.79 (m, 4H), 3.91 (s, 2H), 6.42 (d, 1H), 7.15 (d, 1H).

LRMS : m/z (ES⁺) 220 [MH⁺]

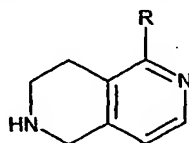
Preparation 110

2-(4-Methyl-1-piperazinyl)-5,6,7,8-tetrahydro[1,6]naphthyridine



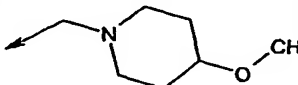
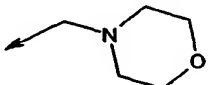
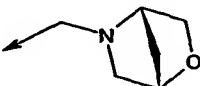
The title compound was obtained in 21% yield from the protected naphthyridine from preparation 56, following the procedure described in preparation 109.

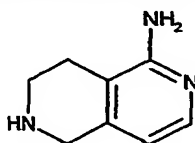
¹H-nmr (CDCl₃, 400MHz) δ: 2.32 (s, 3H), 2.49 (m, 4H), 2.72 (t, 2H), 3.15 (t, 2H), 3.51 (m, 4H), 3.83 (s, 2H), 6.43 (d, 1H), 7.10 (d, 1H). LRMS : m/z (ES⁺) 233 [MH⁺]

Preparations 111 to 118

- Ammonium formate (5-25eq) was added to a solution of the appropriate protected amines (1eq) in methanol. 10% Palladium on charcoal (1:1 w/w eq.) was added portionwise, and the mixture stirred under reflux for 0.5 to 4 hours. The cooled mixture was filtered through Arbocel®, washing through with dichloromethane or dichloromethane:methanol (95:5) and the combined filtrates were evaporated under reduced pressure. The crude products were purified by column chromatography on silica gel using elution gradients of dichloromethane:methanol:0.88 ammonia, to afford the title compounds.

Prep	R	Yield% /Form	Data
111		41 clear oil	¹ H-nmr (CDCl ₃ , 400MHz) δ: 2.22 (s, 6H), 2.84 (t, 2H), 3.18 (t, 2H), 3.52 (s, 2H), 3.98 (s, 2H), 6.80 (d, 1H), 8.24 (d, 1H). LRMS : m/z (ES ⁺) 192 [MH ⁺]
113		69	¹ H-nmr (CDCl ₃ , 400MHz) δ: 1.78 (m, 4H), 2.58 (m, 4H), 2.86 (m, 2H), 3.18 (m, 2H), 3.70 (s, 2H), 3.97 (s, 2H), 6.81 (d, 1H), 8.24 (d, 1H). LRMS : m/z (ES ⁺) 218 [MH ⁺]
114		65 yellow gum	¹ H-nmr (CDCl ₃ , 400MHz) δ: 1.41 (m, 2H), 1.53 (m, 4H), 2.41 (m, 4H), 2.90 (t, 2H), 3.16 (t, 2H), 3.54 (s, 2H), 3.98 (s, 2H), 6.81 (d, 1H), 8.25 (d, 1H). LRMS : m/z (ES ⁺) 254 [MNa ⁺]
115		24 colour -less oil	¹ H-nmr (CDCl ₃ , 400MHz) δ: 1.25 (m, 4H), 1.78 (m, 4H), 2.92 (t, 2H), 3.16 (t, 2H), 2.23 (m, 2H), 3.59 (s, 2H), 3.98 (s, 2H), 6.80 (d, 1H), 8.24 (d, 1H). LRMS : m/z (ES ⁺) 244 [MH ⁺]

Prep	R	Yield%/Form	Data
116		84 orange oil	$^1\text{H-nmr}$ (CDCl_3 , 400MHz) δ : 1.58 (m, 4H), 1.85 (m, 2H), 2.20 (m, 2H), 2.75 (m, 2H), 2.90 (m, 2H), 3.18 (m, 4H), 3.59 (s, 2H), 3.98 (s, 2H), 6.80 (d, 1H), 8.24 (d, 1H). LRMS : m/z (ES^+) 262 [MH^+]
117		75 colour-less oil	$^1\text{H-nmr}$ (CDCl_3 , 400MHz) δ : 2.48 (m, 4H), 2.88 (t, 2H), 3.18 (t, 2H), 3.60 (s, 2H), 3.65 (m, 4H), 3.98 (s, 2H), 6.81 (d, 1H), 8.24 (d, 1H). LRMS : m/z (ES^+) 234 [MH^+]
118		85 oil	$^1\text{H-nmr}$ (CDCl_3 , 400MHz) δ : 1.90 (d, 1H), 2.67 (d, 1H), 2.88 (m, 4H), 3.18 (m, 2H), 3.41 (s, 1H), 3.61 (d, 1H), 3.82 (m, 2H), 3.98 (s, 2H), 4.07 (d, 1H), 4.37 (s, 1H), 6.82 (d, 1H), 8.24 (d, 1H). LRMS : m/z (ES^+) 468 [MNa^+]

Preparation 1195,6,7,8-Tetrahydro[2,6]naphthyridin-1-amine

- 5 A mixture of the protected amine from preparation 68 (234mg, 0.71mmol), ammonium formate (2.34g, 37mmol) and 10% palladium on charcoal (234mg) in methanol (10mL) was heated under reflux for 2 hours. Additional ammonium formate (2.34g, 37mmol) and 10% palladium on charcoal (234mg) were added, and the mixture heated for a further 4 hours. The cooled mixture was diluted with dichloromethane (50mL), filtered
- 10 through Arbocel® and the filtrate concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (93:7:1) as eluant to afford the title compound, as a solid, 21mg.

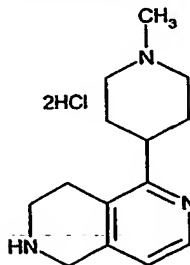
^1H -nmr (CDCl_3 , 400MHz) δ : 2.40 (t, 2H), 3.20 (t, 2H), 3.88 (s, 2H), 4.34 (bs, 2H), 6.38 (d, 1H), 7.82 (d, 1H).

LRMS : m/z (ES^+) 150 [MH^+]

5

Preparation 120

5-(1-Methyl-4-piperidiny)-1,2,3,4-tetrahydro[2,6]naphthyridine dihydrochloride



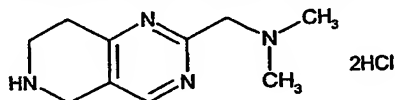
Formic acid (150 μl , 3.92mmol) followed by 10% palladium on charcoal (150mg) were added to a solution of the protected naphthyridine from preparation 67 (630mg, 1.96mmol) in methanol (10mL), and the mixture heated under reflux for 4 hours. Additional 10% palladium on charcoal (350mg) and formic acid (150 μl) were added, and the mixture stirred under reflux for a further 18 hours. The cooled reaction mixture was filtered through Arbocel®, washing through with methanol (300mL), and the combined filtrates evaporated under reduced pressure. The residual oil was dissolved in 1N hydrochloric acid (6mL), and the solution stirred under reflux for 1 hour. The cooled solution was concentrated under reduced pressure, azeotroped with methanol and dichloromethane to afford the title compound as a pale yellow foam, 590mg.

^1H -nmr (CD_3OD , 40MHz) δ : 2.18 (m, 2H), 2.26 (m, 2H), 2.95 (s, 3H), 3.30 (m, 4H), 3.50 (m, 1H), 3.62 (m, 4H), 4.58 (s, 2H), 7.56 (d, 1H), 8.57 (d, 1H).

LRMS : m/z (ES^+) 232 [MH^+]

Preparation 121

N,N-Dimethyl(5,6,7,8-tetrahydropyridof[4,3-*d*]pyrimidin-2-yl)methanamine



Hydrogen chloride gas was bubbled through an ice-cooled solution of the protected amine from preparation 71 (267mg, 0.91mmol) in dichloromethane (15mL), for 10 minutes, and the reaction then stirred for a further 20 minutes at room temperature. The solution was evaporated under reduced pressure, dissolved in methanol (5mL),

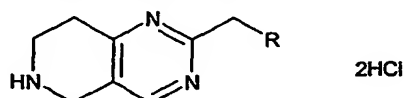
and diluted with ethyl acetate (40mL). The solution was evaporated under reduced pressure to afford the title compound as a buff-coloured solid.

$^1\text{H-nmr}$ (DMSO-d_6 , 400MHz) δ : 2.96 (s, 6H), 3.17 (t, 2H), 3.45 (t, 2H), 4.37 (s, 2H), 4.60 (s, 2H), 8.79 (s, 1H), 10.00-10.20 (bs, 3H). LRMS : m/z (ES^+) 193 [MH^+]

5

Preparations 122 to 125

The following compounds of general structure:

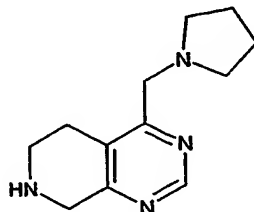


were prepared from the appropriate protected amines following a similar procedure to that described in preparation 121.

10

Prep	R	Form	Data
122		Brown solid	$^1\text{H-nmr}$ (DMSO-d_6 , 400MHz) δ : 2.90 (s, 3H), 3.17 (t, 2H), 3.25 (s, 3H), 3.37-3.60 (m, 4H), 3.72 (t, 2H), 4.36 (s, 2H), 4.60 (bd, 2H), 8.78 (s, 1H), 10.00 (bs, 2H), 10.20 (bs, 1H). LRMS : m/z (ES^+) 237 [MH^+]
124		Tan solid	$^1\text{H-nmr}$ (DMSO-d_6 , 400MHz) δ : 1.60-1.80 (m, 6H), 3.15 (m, 2H), 3.17 (t, 2H), 3.45 (m, 4H), 4.38 (s, 2H), 4.58 (s, 2H), 8.79 (s, 1H), 9.96-10.17 (m, 3H). LRMS : m/z (ES^+) 233 [MH^+]
125		solid	$^1\text{H-nmr}$ (DMSO-d_6 +dropTFAd, 400MHz) δ : 3.10 (m, 4H), 3.36 (m, 2H), 3.52 (m, 2H), 3.81 (m, 4H), 3.94 (m, 4H), 4.30 (m, 2H), 4.69 (s, 2H), 8.67 (s, 1H), 9.85 (bs, 2H). LRMS : m/z (ES^+) 279 [MH^+]

(a)-compound azeotroped with dichloromethane

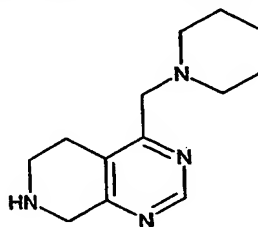
Preparation 1264-(1-Pyrrolidinymethyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine

5 A solution of the protected amine from preparation 69 (395mg, 1.28mmol) in methanol (25mL), was allowed to stand under a nitrogen atmosphere. 10% Palladium on charcoal (395mg), followed by ammonium formate (1.0g, 15.9mmol) was added, and the mixture stirred vigorously under reflux for 30 minutes. The cooled mixture was diluted with dichloromethane (100mL), filtered through Arbocel® and the filtrate concentrated under reduced pressure. The crude product was purified by column chromatography using dichloromethane:methanol:0.88 ammonia (97:3:1) as eluant to afford the title compound as a colourless oil, that crystallised on standing, 174mg.

¹H-nmr (CDCl₃, 400MHz) δ: 1.78 (m, 4H), 2.57 (m, 4H), 2.85 (t, 2H), 3.15 (t, 2H), 3.68 (s, 2H), 4.04 (s, 2H), 8.89 (s, 1H).

LRMS : m/z (ES⁺) 219 [MH⁺]

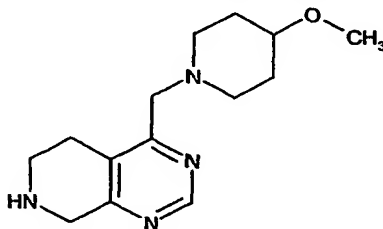
15

Preparation 1274-(1-Piperidinymethyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine

20 The title compound was obtained as an orange oil in 43% yield from the protected amine from preparation 72, following the procedure described in preparation 126.

¹H-nmr (CDCl₃, 400MHz) δ: 1.42 (m, 2H), 1.55 (m, 4H), 2.41 (m, 4H), 2.89 (t, 2H), 3.14 (t, 2H), 3.50 (s, 2H), 4.05 (s, 2H), 8.87 (s, 1H).

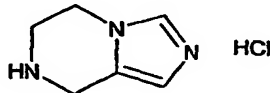
LRMS : m/z (ES⁺) 233 [MH⁺]

Preparation 1284-[(4-Methoxy-1-piperidiny)methyl]-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine

The title compound was obtained in 42% yield as a yellow oil, from the protected amine

¹H-nmr (CDCl₃, 400MHz) δ: 1.56 (m, 2H), 1.84 (m, 2H), 2.24 (m, 2H), 2.73 (m, 2H), 2.88 (t, 2H), 3.15 (t, 2H), 3.20 (m, 1H), 3.32 (s, 3H), 3.53 (s, 2H), 4.05 (s, 2H), 8.87 (s, 1H).

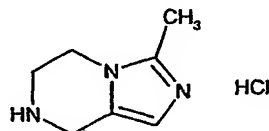
LRMS : m/z (ES⁺) 263 [MH⁺]

Preparation 1295,6,7,8-Tetrahydroimidazo[1,5-a]pyrazine hydrochloride

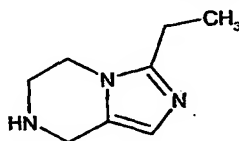
10% Palladium on charcoal (100mg) was added portionwise to a solution of the protected amine from preparation 79 (900mg, 4.22mmol) in methanol (10mL), followed by formic acid (0.25mL), and the reaction stirred under reflux for 5 hours. The cooled mixture was diluted with water (5mL), filtered through Arbocel®, and washed through with methanol (200mL). The filtrate was concentrated under reduced pressure and azeotroped with dichloromethane. The residual oil was dissolved in 1N hydrochloric acid (10mL), and the solution stirred under reflux for 2 hours. The cooled solution was evaporated under reduced pressure and the resulting solid recrystallised from methanol to afford the title compound as a white solid, 500mg.

¹H-nmr (DMSO-d₆, 400MHz) δ: 3.58 (t, 2H), 4.40 (s, 2H), 4.50 (t, 2H), 7.56 (s, 1H), 9.10 (s, 1H).

LRMS : m/z (ES⁺) 125 [MH⁺]

Preparation 1303-Methyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine hydrochloride

- Ammonium formate (3.33g, 52.8mmol) and 10% palladium on charcoal (800mg) were added to a solution of the protected amine from preparation 81 (800mg, 3.52mmol) in methanol (10mL) and 2N hydrochloric acid (0.5mL), and the reaction heated under reflux for 25 hours. The cooled mixture was diluted with water (5mL), then filtered through Arbocel®. The filtrate was evaporated under reduced pressure, and the residual solid purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (100:0:0 to 90:10:1) to give a solid. This was dissolved in 2N hydrochloric acid (10mL), the solution heated under reflux for 2 hours, then cooled and evaporated under reduced pressure, azeotroping with dichloromethane, to afford the title compound as a white solid, 536mg.
- ¹H-nmr (CD₃OD, 400MHz) δ: 2.66 (s, 3H), 3.81 (t, 2H), 4.44 (t, 2H), 4.57 (s, 2H), 7.46 (s, 1H).
- LRMS : m/z (ES⁺) 138 [MH⁺]

Preparation 1313-Ethyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine

- Ammonium formate (2.12g, 33.6mmol) and 10% palladium on charcoal (550mg) were added to a solution of the protected amine from preparation 80 (541mg, 2.24mmol) in methanol (15mL) and 2N hydrochloric acid (0.5mL), and the reaction heated under reflux for 26 hours. The cooled mixture was diluted with water (5mL), then filtered through Arbocel®, washing through with dichloromethane:methanol solution (1:1, 300mL). The filtrate was evaporated under reduced pressure, and the residual solid was dissolved in 2N hydrochloric acid (10mL), the solution heated under reflux for 2 hours, then cooled and evaporated under reduced pressure. The residual orange gum was purified by column chromatography on silica gel using an elution gradient of

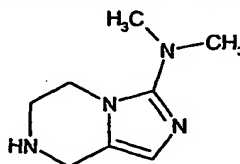
dichloromethane:methanol:0.88 ammonia (97:3:0 to 90:10:1) to give the title compound as an orange solid, 68mg.

^1H -nmr (CD_3OD , 400MHz) δ : 1.24 (t, 3H), 2.67 (q, 2H), 3.15 (t, 2H), 3.88 (t, 2H), 3.95 (s, 2H), 6.59 (s, 1H).

5 LRMS : m/z (ES^+) 138 [MH^+]

Preparation 132

N,N-Dimethyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazin-3-amine



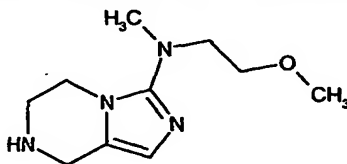
10 Ammonium formate (2.0g, 31.7mmol) and 10% palladium on charcoal (200mg) were added to a solution of the protected amine from preparation 85 (170mg, 0.66mmol) in ethereal hydrochloric acid (2mL, 1M) and methanol (20mL), and the mixture heated under reflux for 20 minutes. The cooled mixture was diluted with dichloromethane (50mL), filtered through Arbocel®, and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (93:7:1) as eluant to afford the title compound as a colourless gum, 72mg.

15 ^1H -nmr (CDCl_3 , 400MHz) δ : 1.70 (bs, 1H), 2.74 (s, 6H), 3.13 (t, 2H), 3.73 (t, 2H), 3.98 (s, 2H), 6.46 (s, 1H).

20 LRMS : m/z (ES^+) 167 [MH^+]

Preparation 133

N-(2-Methoxyethyl)-*N*-methyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazin-3-amine

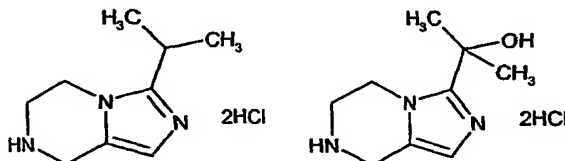


25 The title compound was obtained as a yellow oil, from the protected amine from preparation 86, following the procedure described in preparation 132.

^1H -nmr (CDCl_3 , 400MHz) δ : 2.78 (s, 3H), 3.13 (t, 2H), 3.18 (t, 2H), 3.32 (s, 3H), 3.48 (t, 2H), 3.76 (t, 2H), 3.97 (t, 2H), 6.48 (s, 1H). LRMS : m/z (ES^+) 211 [MH^+]

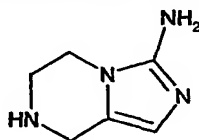
Preparation 1343-Isopropyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine dihydrochloride

and

Preparation 1352-(5,6,7,8-Tetrahydroimidazo[1,5-a]pyrazin-3-yl)-2-propanoldihydrochloride

A mixture of the compounds from preparations 87 and 88 (460mg, 1.47mmol), glacial acetic acid (0.5mL) and 10% palladium on charcoal (300mg) was hydrogenated at 50 psi and 70°C for 36 hours. The cooled mixture was diluted with water (10mL), filtered through Arbocel®, washing through with methanol (500mL). The filtrate was evaporated under reduced pressure, and the residual oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (97:3:0 to 92:8:1) to give an orange oil. This was dissolved in methanol, 1N ethereal hydrochloric acid added, and the mixture evaporated under reduced pressure to give a mixture of the title compounds as a light brown foam, 165mg.

¹H-nmr (CD₃OD, 400MHz) δ: 1.42 (d, 6H), 1.71 (s, 6H), 3.45 (m, 1H), 3.78 (m, 2H), 3.78 (m, 2H), 4.50 (m, 2H), 4.58 (m, 2H), 4.58 (m, 2H), 4.80 (m, 2H), 7.46 (s, 1H).

Preparation 1365,6,7,8-Tetrahydroimidazo[1,5-a]pyrazin-3-amine

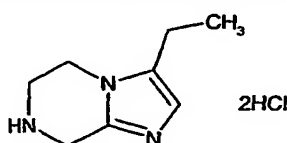
10% Palladium on charcoal (200mg) and ammonium formate (2g) were added carefully to a solution of the compound from preparation 84 (152mg, 0.6mmol) in 1N ethereal hydrochloric acid (2mL) and methanol (20mL). The mixture was heated under reflux for 1.5 hours, then cooled. Additional 1N ethereal hydrochloric acid (1mL), 10% palladium on charcoal (200mg) and ammonium formate (2g) were added, and the mixture heated under reflux for a further 20 minutes. The cooled mixture was diluted with

dichloromethane (50mL), filtered through Arbocel®, and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (93:7:1 to 80:20:2) to afford the title compound as an oil, 35mg.

- 5 ¹H-nmr (DMSO-d₆, 400MHz) δ: 3.12 (t, 2H), 3.57 (t, 2H), 3.87 (s, 2H), 6.27 (s, 1H).
LRMS : m/z (ES⁺) 139 [MH⁺]

Preparation 137

3-Ethyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine dihydrochloride



10

A mixture of the protected amine from preparation 92 (605mg, 2.12mmol), acetic acid (8mL), and 1N ethereal hydrobromic acid (30mL) in toluene (25mL) was stirred at 100°C for 4 hours. The mixture was cooled, concentrated under reduced pressure, and azeotroped with toluene (2x25mL). The residue was dissolved in 1N ethereal hydrochloric acid, then evaporated under reduced pressure to afford the title compound as a tan coloured solid, 405mg.

15

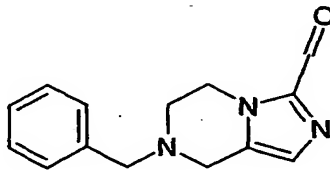
¹H-nmr (DMSO-d₆, 400MHz) δ: 1.10 (t, 3H), 2.60 (m, 2H), 3.60 (m, 2H), 4.32 (m, 2H) 4.62 (s, 2H), 7.50 (s, 1H).

LRMS : m/z (ES⁺) 152 [MH⁺]

20

Preparation 138

7-Benzyl-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazine-3-carbaldehyde



25

n-Butyllithium (1.6M in hexane, 9 ml, 14.4 mmol) was added to the imidazopyrazine from preparation 79 (2.8 g, 13.13 mmol) in tetrahydrofuran (20 ml) under a nitrogen atmosphere at -78°C at a rate that maintained the reaction temperature below -70°C. The mixture was warmed to 0°C and was stirred for 10 minutes and then cooled to -78°C. N,N-Dimethylformamide (1.5 ml, 19.4 mmol) was added dropwise and the mixture was warmed to 0°C and was stirred for 10 minutes. Saturated sodium

hydrogen carbonate solution (40 ml), then water (100 ml) were added and the aqueous solution was extracted with ethyl acetate (100 ml). The organic solution was washed with water (50 ml), then brine (50 ml), dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ethyl acetate in pentane as eluant (gradient from 70:30 to 90:10) to give the title compound as a yellow solid (2.67 g).

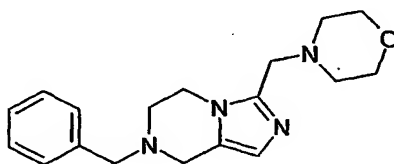
¹H-nmr (CDCl₃, 400MHz) δ: 2.89 (t, 2H), 3.72 (m, 4H), 4.44 (t, 2H), 7.02 (s, 1H), 7.35 (m, 5H), 9.72 (s, 1H)

LRMS: m/z (ES⁺) 264 [MNa⁺]

10

Preparation 139

7-Benzyl-3-morpholin-4-ylmethyl-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazine

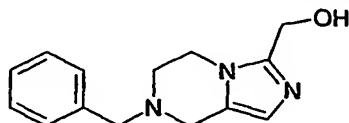


Morpholine (260 μl, 3.0 mmol) was added to the aldehyde from preparation 138 in tetrahydrofuran (10 ml) under a nitrogen atmosphere and the mixture was stirred for 1 hour. Sodium triacetoxymethylborohydride (790 mg, 3.73 mmol) was added portionwise and the reaction mixture was stirred at room temperature for 16 hours. Water (20 ml) was added and the solution was extracted with ethyl acetate (2x100 ml). The combined organic solutions were dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 1:99 to 5:95) to give the title compound as a golden oil (680 mg).

¹H-nmr (CDCl₃, 400MHz) δ: 2.46 (m, 4H), 2.84 (t, 2H), 3.55 (s, 2H), 3.66 (m, 4H), 4.06 (t, 2H), 6.65 (s, 1H), 7.31 (m, 5H)

LRMS: m/z (ES⁺) 335 [MNa⁺]

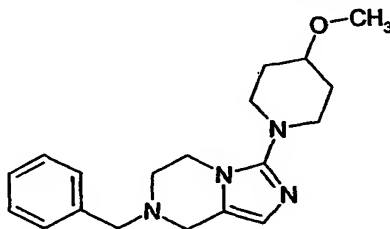
25

Preparation 140(7-Benzyl-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-3-yl)-methanol

Sodium borohydride (250 mg, 6.6 mmol) was added portionwise to the aldehyde from preparation 138 (1.45 g, 6 mmol) in methanol (25 ml) under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 hour and further sodium borohydride (45 mg, 2 mmol) was added. The mixture was stirred at room temperature for 30 minutes and saturated sodium hydrogen carbonate solution (40 ml) and water (40 ml) were added. The aqueous mixture was extracted with ethyl acetate (3x100 ml) and the combined organic solutions were dried over magnesium sulphate and evaporated under reduced pressure. The residue was co-evaporated with dichloromethane (x2) and the residue was dried under vacuum to give the title compound as a gum (1.45 g)

¹H-nmr (CDCl₃, 400MHz) δ: 2.86 (t, 2H), 3.62 (s, 2H), 3.70 (s, 2H), 4.07 (t, 2H), 4.61 (s, 2H), 6.62 (s, 1H), 7.32 (m, 5H)

LRMS: m/z (ES⁺) 266 [MNa⁺]

Preparation 1417-Benzyl-3-(4-methoxy-piperidin-1-yl)-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazine

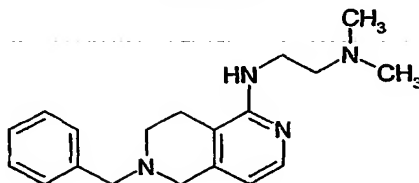
A stirred mixture of the bromo compound from preparation 83 (584 mg, 2 mmol) 4-methoxypiperidine (3 g, 26 mmol) and tetrakis(triphenylphosphine)palladium(0) (46 mg, 0.04 mmol) was purged with argon and then heated to 150°C for 17 hours. The reaction mixture was cooled to room temperature and partitioned between dichloromethane (100 ml) and water (100 ml). The organic phase was separated, dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol in ethyl acetate as eluant (gradient from 2:98 to 6:94). The material obtained was dissolved in dichloromethane (50 ml), washed with 5% sodium carbonate solution (50 ml), water (50 ml) dried over

magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol in ethyl acetate as eluant (gradient from 2:98 to 6:94) to give the title compound as a yellow oil (202 mg).

¹H-nmr (CDCl₃, 400MHz) δ: 1.65 (m, 2H), 2.02 (m, 2H), 2.78 (t, 2H), 2.88 (m, 2H), 3.25 (m, 3H), 3.37 (s, 3H), 3.62 (s, 2H), 3.67 (s, 2H), 3.79 (t, 2H), 6.45 (s, 1H), 7.30 (m, 5H)
LRMS: m/z (ES⁺) 327 [MH⁺]

Preparation 142

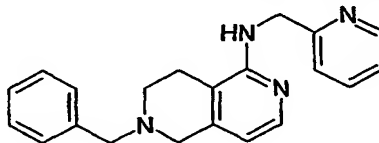
N'-(6-Benzyl-5,6,7,8-tetrahydro-[2,6]naphthyridin-1-yl)-N,N-dimethyl-ethane-1,2-
diamine



A mixture of the bromo compound from preparation 34 (1 g, 3.3 mmol) and N,N-dimethylethylenediamine (5 ml) were heated at 140°C in an autoclave for 20 hours. The mixture was cooled to room temperature and was added to 0.05M sodium hydroxide solution. The solution was extracted with dichloromethane (3x60 ml). The combined organic solutions were dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol and ammonium hydroxide in dichloromethane as eluant (gradient from 0:1:99 to 20:1:79) to give the title compound as a yellow oil (971 mg).
¹H-nmr (CDCl₃, 400MHz) δ: 2.26 (s, 6H), 2.47 (t, 2H), 2.55 (t, 2H), 2.80 (t, 2H), 3.50 (m, 4H), 3.68 (s, 2H), 4.80 (s, 1H), 6.23 (d, 1H), 7.33 (m, 5H), 7.88 (d, 1H)
LRMS: m/z (ES⁺) 311 [MH⁺]

Preparation 143

(6-Benzyl-5,6,7,8-tetrahydro-[2,6]naphthyridin-1-yl)-pyridin-2-ylmethyl-amine

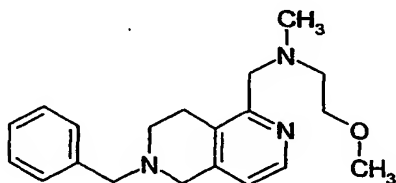


The bromo compound from preparation 34 (303 mg, 1 mmol) was mixed with 2-aminomethylpyrimidine (2 ml) and the mixture was heated at 170 °C under a nitrogen atmosphere for 5 hours. The reaction mixture was cooled and partitioned between

ethyl acetate and 0.02 M sodium hydroxide solution. The organic solution was dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using dichloromethane and ethyl acetate and then methanol in ethyl acetate as eluant (gradient from 100:0 to 0:100) dichloromethane and ethyl acetate followed by methanol in ethyl acetate 0:100 to 5:95) to give the title compound as a pale yellow oil that crystallised on standing (216 mg).
LRMS: m/z (ES⁺) 331 [MH⁺]

Preparation 144

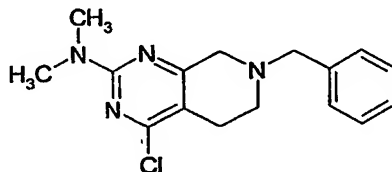
(6-Benzyl-5,6,7,8-tetrahydro-[2,6]naphthyridin-1-ylmethyl)-(2-methoxy-ethyl)-methyl-amine



Acetic acid (480 mg, 8 mmol) was added to a solution of the aldehyde from preparation 35 and N-(2-methoxyethyl)methylamine (356 mg, 4 mmol) in tetrahydrofuran (20 ml) and the mixture was stirred for 10 minutes. Sodium triacetoxyborohydride (2.12 g, 10 mmol) was added and the mixture was stirred at room temperature for 2.5 hours. 2M Hydrochloric acid was added and the mixture was basified with 1M sodium hydroxide and extracted with ethyl acetate. The combined organic solutions were dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 0:100 to 10:90) to give the title compound as a yellow oil (544 mg).

¹H-nmr (CDCl₃, 400MHz) δ: 2.27 (s, 3H), 2.66 (t, 2H), 2.79 (t, 2H), 3.00 (t, 2H), 3.28 (s, 3H), 3.48 (t, 2H), 3.60 (s, 2H), 3.66 (s, 2H), 3.68 (s, 2H), 6.80 (d, 1H), 7.34 (m, 5H), 8.25 (d, 1H)

LRMS: m/z (ES⁺) 326 [MH⁺]

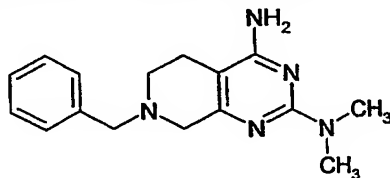
Preparation 145(7-Benzyl-4-chloro-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-2-yl)-dimethyl-amine

1-Benzyl-3-oxo-piperidine-4-carboxylic acid ethyl ester (10 g, 38.3 mmol) was added to
5 a mixture of dimethyl guanidinium sulphate (4.6 g, 25 mmol) and potassium carbonate (9.28 g, 67 mmol) in methanol and the reaction mixture was stirred at room temperature for 48 hours. The mixture was filtered and the solid obtained was recrystallised from ethanol.

The material isolated was dissolved in phosphorous oxychloride (20 ml) and heated at
10 90°C for 1 hour. The mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane (50 ml) and was added to sodium hydrogen carbonate solution. The aqueous layer was extracted with dichloromethane (2x50 ml) and the combined organic solutions were dried over magnesium sulphate and evaporated under reduced pressure to give the title compound as a brown oil (3.03 g).

15 ¹H-nmr (CDCl₃, 400MHz) δ: 2.70 (m, 4H), 3.12 (s, 6H), 3.48 (s, 2H), 3.68 (s, 2H), 7.33 (m, 5H)

LRMS: *m/z* ES⁺ 303, 305 [MH⁺]

Preparation 14620 7-Benzyl-N²,N²-dimethyl-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidine-2,4-diamine

Ammonia was bubbled through a solution of the chloro compound from preparation 145 (1.51 g, 5 mmol) in dimethylsulphoxide (20 ml) to give a saturated solution and the mixture was heated at 140°C in an autoclave for 18 hours. The reaction mixture was
25 cooled to room temperature and was dissolved in ethyl acetate. The organic solution was washed with water and brine (x2) and then was dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 0:100 to 6:94) to give the title compound as a brown solid (0.54 g).

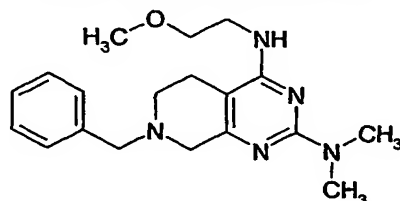
¹H-nmr (DMSO-d₆, 400MHz) δ: 2.40 (t, 2H), 2.73 (t, 2H), 3.05 (s, 6H), 3.41 (s, 2H), 3.67 (s, 2H), 4.45 (s, 2H), 7.33 (m, 5H)

LRMS: *m/z* ES⁺ 284 [MH⁺]

5

Preparation 147

7-Benzyl-N⁴-(2-methoxy-ethyl)-N²*,N²*-dimethyl-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidine-2,4-diamine



The chloro compound from preparation 145 (1.51 g, 5 mmol) and 2-methoxyethylamine (2 ml, 23 mmol) were dissolved in ethanol (20 ml) and the solution was heated under reflux for 48 hours. The solvent was evaporated under reduced pressure and the residue was diluted with 2-methoxyethylamine (6 ml, 69 mmol) and was heated under reflux for 8 hours. The reaction mixture was cooled to room temperature and was added to ethyl acetate. The solution was washed with 0.1M sodium hydroxide solution and brine, dried over magnesium sulphate and evaporated under reduced pressure to give the title compound (1.57 g).

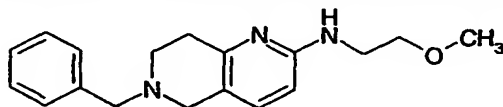
¹H-nmr (CDCl₃, 400MHz) δ: 2.35 (t, 2H), 2.73 (t, 2H), 3.07 (s, 6H), 3.35 (s, 3H), 3.40 (s, 2H), 3.53 (t, 2H), 3.66 (m, 4H), 4.62 (t, 1H), 7.23 (m, 1H), 7.31 (m, 2H), 7.35 (d, 2H)

LRMS: *m/z* ES⁺ 342 [MH⁺]

20

Preparation 148

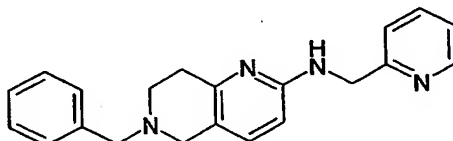
(6-Benzyl-5,6,7,8-tetrahydro-[1,6]naphthyridin-2-yl)-(2-methoxy-ethyl)-amine



Copper (II) sulphate (200 mg) was added to a solution of 6-benzyl-2-chloro-5,6,7,8-tetrahydro-[1,6]naphthyridine (4.5 g, 17.4 mmol)(see reference WO9830560 Example 33 b) in 2-methoxyethylamine and the mixture was heated under reflux for 20 hours. The mixture was evaporated under reduced pressure and the residue was partitioned between dichloromethane (100 ml) and water (50 ml). The aqueous phase was extracted with dichloromethane (2x50 ml) and the combined organic phases were dried over magnesium sulphate and evaporated under reduced pressure. The residue was

purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 1:99 to 3:97) to give the title compound as an orange oil (1.32 g).
LRMS: m/z ES⁺ 298.2 [MH⁺]

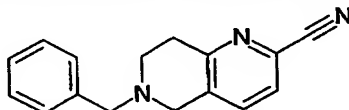
5

Preparation 149(6-Benzyl-5,6,7,8-tetrahydro-[1,6]naphthyridin-2-yl)-pyridin-2-ylmethyl-amine

The title compound was obtained from 6-benzyl-2-chloro-5,6,7,8-tetrahydro-[1,6]naphthyridine (see reference WO9830560 Example 33b) and 2-aminomethylpyridine in 50% yield following the procedure described in preparation 148.

LRMS: m/z ES⁺ 331.2 [MH⁺]

15

Preparation 1506-Benzyl-5,6,7,8-tetrahydro-[1,6]naphthyridine-2-carbonitrile

6-Benzyl-2-chloro-5,6,7,8-tetrahydro-[1,6]naphthyridine (129 mg, 0.5 mmol) (See Reference WO9830560 Example 33b) was added to zinc cyanide (58.7 mg, 0.5 mmol), lithium chloride (27 mg, 0.65 mmol) and tetrakis(triphenylphosphine)palladium (0) (35 mg, 0.03 mmol) in N,N-dimethylformamide (3 ml). The mixture was purged with argon and was heated at 100°C for 17 hours. The reaction mixture was cooled to room temperature and a further quantity of tetrakis(triphenylphosphine)palladium (0) (35 mg, 0.03 mmol) was added and the mixture was heated at 125°C for 3 hours. The reaction mixture was cooled to room temperature and a further quantity of tetrakis(triphenylphosphine)palladium (0) (35 mg, 0.03 mmol) was added and the mixture was heated at 125°C for 3 hours. The reaction mixture was cooled to room temperature and was partitioned between ethyl acetate (40 ml) and water (40 ml). The phases were separated and the organic phase was washed with water (3x30 ml) dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ethyl acetate in pentane as eluant (33:67) to give the title compound as a brown gum (97 mg).

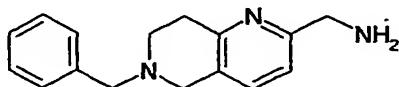
¹H-nmr (CDCl₃, 400MHz) δ: 2.88 (t, 2H), 3.09 (t, 2H), 3.68 (s, 2H), 3.73 (s, 2H), 7.23 (m, 7H)

LRMS: *m/z* ES⁺ 250 [MH⁺].

5

Preparation 151

(6-Benzyl-5,6,7,8-tetrahydro-[1,6]naphthyridin-2-yl)-methylamine



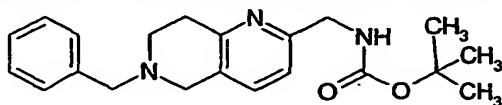
Anhydrous cobalt chloride (389 mg, 3 mmol) was added to the nitrile from preparation 150 (373 mg, 1.5 mmol) in methanol (10 ml) and the mixture was stirred at room temperature for 10 minutes. Sodium borohydride (567 mg, 15 mmol) was added portionwise over 15 minutes and the reaction mixture was stirred at room temperature for 1.5 hours. 3N Hydrochloric acid (7 ml) was added dropwise over 10 minutes and the mixture was stirred at room temperature for 20 minutes. The solution was neutralised by addition of concentrated aqueous ammonia and the mixture was stirred at room temperature for 72 hours. Silica gel (10 g) was added and the mixture was evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ammonium hydroxide and methanol in dichloromethane as eluant (2:15:85). The material obtained was co evaporated with methanol and then with dichloromethane to give the title compound as a pale brown gum (135 mg).

¹H-nmr (CDCl₃, 400MHz) δ: 2.86 (t, 2H), 3.00 (t, 2H), 3.60 (s, 2H), 3.70 (s, 2H), 3.90 (s, 2H), 7.30 (m, 7H)

LRMS: *m/z* (ES⁺) 254 [MH⁺]

Preparation 152

(6-Benzyl-5,6,7,8-tetrahydro-[1,6]naphthyridin-2-ylmethyl)-carbamic acid *tert*-butyl ester



Di-*tert*-butyl dicarbonate (300 mg, 1.37 mmol) in dichloromethane (2 ml) was added to the amine from preparation 151 (288 mg, 1.14 mmol) in dichloromethane (10 ml) and the mixture was stirred at room temperature for 72 hours. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel using ammonium hydroxide and methanol in dichloromethane as eluant (0.5:5:95). The material obtained was further purified by chromatography on silica gel using

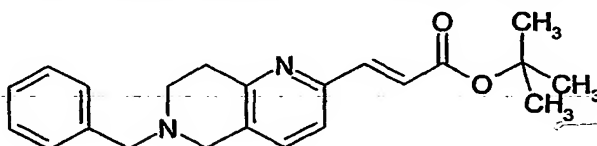
ammonium hydroxide and propan-2-ol in pentane as eluant (gradient from 0.5:10:90 to 0.7:15:85). The material isolated was co-evaporated with methanol to give the title compound as a colourless gum (251 mg).

¹H-nmr (CDCl₃, 400MHz) δ: 1.46 (s, 9H), 2.95 (t, 2H), 3.00 (t, 2H), 3.60 (d, 2H), 3.71 (s, 2H), 4.35 (d, 2H), 5.41 (s, 1H), 7.00 (d, 1H), 7.30 (m, 6H)

LRMS: *m/z* (ES⁺) 354 [MH⁺]

Preparation 153

tert-Butyl (2*E*)-3-(6-benzyl-5,6,7,8-tetrahydro[1,6]naphthyridin-2-yl)-2-propenoate



10

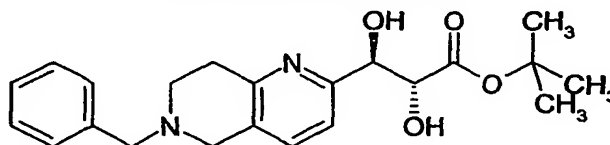
Tri-*tert*-butylphosphine (3.0 g, 15.28 mmol) was added to a solution of tris(dibenzylideneacetone)dipalladium (4.2 g, 4.63 mmol) in 1,4-dioxane (45 ml), under argon, and the solution stirred for 30 minutes at room temperature. This solution was then added to a mixture of 6-benzyl-2-chloro-5,6,7,8-tetrahydro[1,6]naphthyridine (WO 9830560 Example 33b) (12 g, 46.3 mmol) and *tert*-butylacrylate (20.3 ml, 139 mmol) in triethylamine (45 ml), and the reaction was stirred under reflux for 17 hours. The cooled mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate (300 ml) and water (300 ml) and this mixture filtered through Arbocel®. The pH of the mixture was adjusted to 8 using sodium bicarbonate, the phases separated, and the aqueous layer re-extracted with ethyl acetate (2x100 ml). The combined organic solutions were dried over magnesium sulphate and evaporated under reduced pressure. The crude product was pre-adsorbed onto silica gel, and purified by column chromatography using an elution gradient of cyclohexane: ethyl acetate (84:16 to 66:34) to afford the title compound as an orange-red oil, (15.8 g).

20

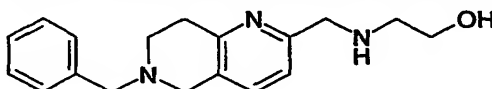
¹H-nmr (CDCl₃, 400MHz) δ: 1.50 (s, 9H), 2.82 (t, 2H), 3.02 (t, 2H), 3.61 (s, 2H), 3.70 (s, 2H), 6.75 (d, 1H), 7.18 (d, 1H), 7.26 (m, 2H), 7.35 (m, 4H), 7.55 (d, 1H).

25

LRMS: *m/z* (ES⁺) 373 [MNa⁺]

Preparation 154*tert*-Butyl (2*R*,3*R*)-3-(6-benzyl-5,6,7,8-tetrahydro[1,6]naphthyridin-2-yl)-2,3-dihydroxypropanoate

- 5 Osmium tetroxide (8.3 ml, 2.5%wt.in *tert*-butanol) was added dropwise to a mixture of the compound from preparation 153 (11.3 g, 32.2 mmol), N-methylmorpholine N-oxide (4.15 g, 35.4 mmol) in water (80 ml) and acetone (160 ml), and the reaction was stirred at room temperature for 72 hours. The mixture was concentrated under reduced pressure, and the residue azeotroped with acetone. The crude product was purified by
- 10 column chromatography on silica gel using an elution gradient of cyclohexane: ethyl acetate (80:25 to 25:75), to afford the title compound as a gum (7.2 g).
- ¹H-nmr (DMSO-d₆, 400MHz) δ: 1.38 (s, 9H), 2.77 (m, 2H), 2.81 (m, 2H), 3.52 (s, 2H), 3.62 (s, 2H), 4.20 (d, 1H), 4.78 (d, 1H), 4.82 (d, 1H), 5.40 (d, 1H), 7.22 (m, 2H), 7.30 (m, 4H), 7.38 (d, 1H).
- 15 LRMS : m/z (ES⁺) 407 [MNa⁺]

Preparation 1552-[(6-Benzyl-5,6,7,8-tetrahydro[1,6]naphthyridin-2-yl)methyl]amino}ethanol

- 20 Acetic acid (368.7 mg, 6.14 mmol) and ethanolamine (187.5 mg, 3.07 mmol) were added dropwise to a solution of the aldehyde from preparation 29b (595 mg, 2.36 mmol), and the mixture purged with argon, then heated under reflux for 2 hours. Sodium triacetoxyborohydride (1 g, 4.72 mmol) was added to the cooled solution, and the reaction stirred at room temperature for 17 hours. 2M Hydrochloric acid (12 ml) was
- 25 added, the solution stirred for 15 minutes, then partitioned between dichloromethane (150 ml) and water (150 ml), and the layers separated. The pH of the aqueous layer was adjusted to 12 using 5% aqueous sodium carbonate solution, re-partitioned with the separated organic phase, and further extracted with dichloromethane (3x60 ml). These combined organic solutions were dried over magnesium sulphate and
- 30 evaporated under reduced pressure. The residual oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol:

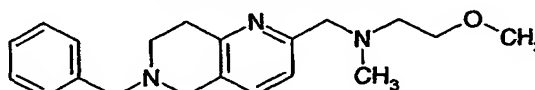
0.88 ammonia (97:3:0.2 to 90:10:10) to afford the title compound as a colourless oil (450mg).

¹H-nmr (CDCl₃, 400MHz) δ: 2.76 (m, 4H), 3.04 (t, 2H), 3.60 (s, 2H), 3.62 (t, 2H), 3.72 (s, 2H), 3.90 (s, 2H), 7.02 (d, 1H), 7.25 (m, 6H).

5 LRMS: m/z (ES⁺) 320 [MNa⁺]

Preparation 156

N-[(6-Benzyl-5,6,7,8-tetrahydro[1,6]naphthyridin-2-yl)methyl]-2-methoxy-N-methylethanamine



10

The title compound was obtained as a yellow oil in 89% yield from the aldehyde from preparation 29b and N-(2-methoxyethyl)methylamine, following a similar procedure to that described in preparation 155.

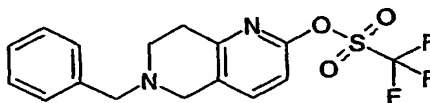
¹H-nmr (CDCl₃, 400MHz) δ: 2.30 (s, 3H), 2.64 (t, 2H), 2.83 (t, 2H), 3.01 (t, 2H), 3.21 (s, 3H), 3.51 (t, 2H), 3.59 (s, 2H), 3.66 (s, 2H), 3.69 (s, 2H), 7.20-7.38 (m, 7H).

15

LRMS: m/z (ES⁺) 348 [MNa⁺]

Preparation 157

6-Benzyl-5,6,7,8-tetrahydro[1,6]naphthyridin-2-yl trifluoromethanesulfonate



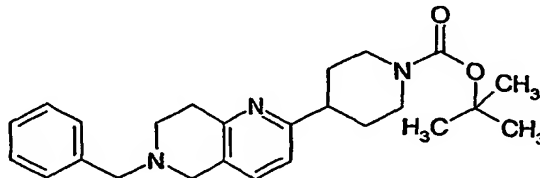
20

Trifluoromethanesulphonic anhydride (770 μl, 4.58 mmol) was added dropwise to a cooled (-30°C) solution of the compound from preparation 27 (1 g, 4.16 mmol) and triethylamine (640 μl, 4.58 mmol) in dichloromethane (20 ml), so as to maintain the temperature below -20°C. The solution was then allowed to warm slowly to room temperature and stirred for a further 2 hours. The solution was diluted with dichloromethane (30 ml), washed with water (10 ml), dried over magnesium sulphate and evaporated under reduced pressure. The residual brown oil was purified by column chromatography on silica gel using an elution gradient of pentane: dichloromethane: methanol (5:95:0 to 0:100:0 to 0:97:3) to afford the title compound as an orange oil (980mg).

25

30

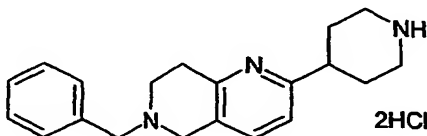
¹H-nmr (CDCl₃, 400MHz) δ: 2.84 (t, 2H), 3.00 (t, 2H), 3.62 (s, 2H), 3.71 (s, 2H), 6.91 (d, 1H), 7.25-7.40 (m, 5H), 7.43 (d, 1H). LRMS: m/z (ES⁺) 373 [MH⁺]

Preparation 158*tert*-Butyl 4-(6-benzyl-5,6,7,8-tetrahydro[1,6]naphthyridin-2-yl)-1-piperidinecarboxylate

A mixture of 1,2-dibromoethane (22 μ l, 0.26 mmol) and activated zinc (640 mg, 9.80 mmol) in N,N-dimethylformamide (1.5 ml) was heated to 50°C for 5 minutes, then allowed to cool to room temperature. Trimethylsilylchloride (32.7 μ l, 0.26 mmol) was added, the mixture heated again to 50°C, re-cooled to room temperature and *tert*-butyl 4-iodo-1-piperidinecarboxylate (EP 1078928 preparation 15-2) (2.0 g, 6.45 mmol) added. This mixture was re-heated to 50°C for 5 minutes, cooled again, and a solution of the compound from preparation 157 (960 mg, 2.58 mmol) in N,N-dimethylformamide (1 ml), followed by tris(dibenzylideneacetone)dipalladium (0) (29.6 mg, 0.05 mmol) and tri(2-furyl)phosphine (24 mg, 0.10 mmol) added and the reaction mixture stirred at 60°C for 2 hours. The cooled mixture was partitioned between water (15 ml) and dichloromethane (50 ml), filtered through Arbocel® and the filtrate separated. The aqueous phase was extracted with dichloromethane (30 ml), and the combined organic solutions dried over magnesium sulphate and evaporated under reduced pressure. The residual orange oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol (100:0 to 96.5:3.5) to afford the title compound as an orange oil (717mg).

¹H-nmr (CDCl₃, 400MHz) δ : 1.45 (s, 9H), 1.63 (m, 2H), 1.87 (m, 2H), 2.84 (m, 4H), 3.00 (m, 2H), 3.58 (s, 2H), 3.69 (s, 2H), 3.83 (m, 1H), 4.22 (bs, 2H), 6.88 (d, 1H), 7.20 (d, 1H), 7.32 (m, 5H).

LRMS: m/z (ES⁺) 430 [MNa⁺]

Preparation 1596-Benzyl-2-(4-piperidiny)-5,6,7,8-tetrahydro[1,6]naphthyridine dihydrochloride

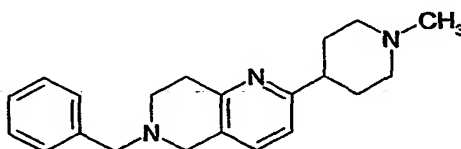
An ice-cooled solution of the protected amine from preparation 158 (700 mg, 1.72 mmol) in dichloromethane (20 ml) was saturated with hydrogen chloride, and the

solution then stirred for 2 hours at 0°C. The reaction mixture was then degassed under nitrogen and evaporated under reduced pressure to afford the title compound as an orange foam (654 mg).

¹H-nmr (CD₃OD, 400MHz) δ: 2.10 (m, 2H), 2.22 (m, 2H), 3.18 (m, 2H), 3.33 (s, 2H),
5 3.53 (m, 4H), 3.80 (m, 1H), 4.58 (m, 4H), 7.53 (m, 4H), 7.63 (m, 3H).
LRMS: m/z (ES⁺) 308 [MH⁺]

Preparation 160

6-Benzyl-2-(1-methyl-4-piperidiny)-5,6,7,8-tetrahydro[1,6]naphthyridine

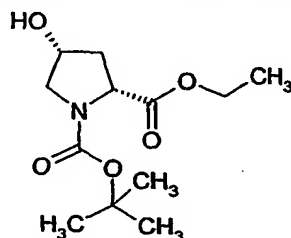


10

Triethylamine (471 μl, 3.37 mmol) and formaldehyde (37% w/w solution, 273 mg, 3.37 mmol) were added to a suspension of the amine from preparation 159 (641 mg, 1.69 mmol) in acetonitrile (10 ml), and the solution stirred at room temperature for 1 hour. Sodium triacetoxyborohydride (1.79 g, 3.37 mmol) was then added and the reaction
15 stirred at room temperature for 18 hours. The mixture was neutralised using saturated sodium bicarbonate solution, then extracted using dichloromethane (3x50 ml). The combined organic solutions were dried over magnesium sulphate and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol: 0.88 ammonia
20 (93:7:0.2 to 91:9:0.6) to afford the title compound as an orange solid (342mg).

¹H-nmr (CDCl₃, 400MHz) δ: 1.80-2.00 (m, 4H), 2.15 (m, 2H), 2.36 (s, 3H), 2.67 (m, 1H), 2.84 (t, 2H), 3.00 (m, 4H), 3.58 (s, 2H), 3.69 (s, 2H), 6.93 (d, 1H), 7.28 (m, 6H).

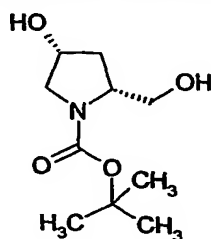
LRMS: m/z (ES⁺) 322 [MH⁺]

Preparation 1611-tert-Butyl 2-ethyl (2R,4R)-4-hydroxy-1,2-pyrrolidinedicarboxylate

Triethylamine (0.27 ml, 2.05 mmol) followed by di-*tert*-butyl dicarbonate (223 mg, 1.02 mmol) were added to a solution of ethyl (2*R*,4*R*)-4-hydroxy-2-pyrrolidinecarboxylate hydrochloride (J. Org. Chem. 1990; 1684) (200 mg, 1.02 mmol) in 1,4-dioxane (5 ml) and water (5 ml), and the reaction stirred at room temperature for 4 hours. The mixture was extracted with ethyl acetate (50 ml), and the organic solution washed sequentially with 0.25M hydrochloric acid (50 ml), water (50 ml) and brine (50 ml). The solution was then dried over magnesium sulphate and evaporated under reduced pressure to afford the title compound (110mg).

¹H-nmr (CDCl₃, 400MHz) δ: 1.24 (t, 3H), 1.42 (s, 9H), 2.20 (m, 2H), 3.52 (m, 2H), 4.23 (q, 2H), 4.35 (m, 2H).

LRMS: m/z (ES⁺) 282 [MNa⁺]

Preparation 162*tert*-Butyl (2*R*,4*R*)-4-hydroxy-2-(hydroxymethyl)-1-pyrrolidinecarboxylate

Lithium borohydride (1.4 ml, 2M in tetrahydrofuran, 2.8 mmol) was added dropwise to an ice-cooled solution of the ester from preparation 161 (210 mg, 0.81 mmol) in tetrahydrofuran (10 ml), the solution stirred for an hour at 0°C, and a further hour at room temperature. The solution was re-cooled to 0°C, water carefully added, followed by 2N hydrochloric acid. The mixture was then warmed to room temperature and extracted with ethyl acetate (3x100 ml). The combined organic solutions were washed with 1N sodium hydroxide solution, brine (100 ml), then dried over magnesium sulphate and evaporated under reduced pressure to afford the title compound (100 mg).

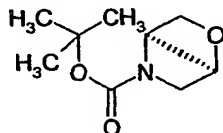
¹H-nmr (CDCl₃, 400MHz) δ: 1.39 (s, 9H), 1.80 (m, 1H), 2.25 (m, 1H), 3.36 (m, 3H), 3.98 (dd, 2H), 4.23 (m, 1H).

LRMS: m/z (ES⁻) 216 [M-H]

5

Preparation 163

tert-Butyl (1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate



Diisopropyl azodicarboxylate (0.5 ml, 2.53 mmol) was added dropwise to an ice-cooled solution of the diol from preparation 162 (500 mg, 2.30 mmol) and triphenylphosphine (664 mg, 2.53 mmol) in dichloromethane (50 ml). Once addition was complete, the reaction was stirred at room temperature for 18 hours. The mixture was partitioned between dichloromethane (100 ml) and water (100 ml), and the layers separated. The aqueous phase was extracted with further dichloromethane (100 ml), and the combined organic solutions dried over magnesium sulphate and evaporated under reduced pressure. The residue was triturated with cyclohexane, the precipitate filtered, and the filtrate evaporated under reduced pressure. This product was purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol (100:0 to 91:9) to afford the title compound (200mg).

¹H-nmr (CDCl₃, 400MHz) δ: 1.43 (s, 9H), 1.82 (m, 2H), 3.29 (m, 2H), 3.83 (m, 2H), 4.48 (m, 2H).

20

LRMS: m/z (ES⁺) 222 [MNa⁺]

Preparation 164

(1R,4R)-2-Oxa-5-azabicyclo[2.2.1]heptane hydrochloride

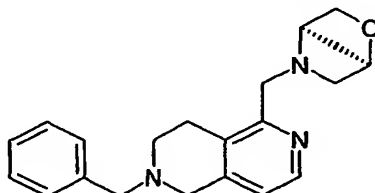


25

An ice-cooled solution of the compound from preparation 163 (200 mg, 1.0 mmol) in dichloromethane (10 ml) was saturated with hydrogen chloride, and the solution then stirred at room temperature for 1 hour. The mixture was concentrated under reduced pressure and the residue azeotroped with diethyl ether to afford the title compound.

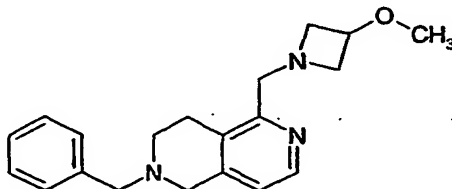
¹H-nmr (DMSO-d₆, 400MHz) δ: 1.83 (d, 1H), 1.91 (d, 1H), 3.10 (s, 2H), 3.64 (d, 1H), 3.92 (d, 1H), 4.35 (s, 1H), 4.61 (s, 1H), 9.22 (s, 2H)

30

Preparation 165(1*R*,4*R*)-5-[(6-benzyl-5,6,7,8-tetrahydro[2,6]naphthyridin-1-yl)methyl]-2-oxa-5-azabicyclo[2.2.1]heptane

- 5 Sodium triacetoxyborohydride (418 mg, 1.98 mmol) was added to a solution of the aldehyde from preparation 35 (211 mg, 1.25 mmol), the amine hydrochloride from preparation 164 (170 mg, 1.25 mmol), sodium acetate (72 mg, 0.88 mmol), and acetic acid (50 μ l, 8.7 mmol) in tetrahydrofuran (10 ml), and the reaction was stirred at room temperature for 4 hours. The solution was diluted with water (15 ml) and 0.88 ammonia:
- 10 (15 ml), and the mixture then extracted with ethyl acetate. The organic extract was washed with brine, dried over magnesium sulphate and concentrated under reduced pressure. The residual oil was purified by column chromatography on silica gel using dichloromethane: methanol (100:0 to 92.5:7.5) to afford the title compound as a yellow oil, 127mg.
- 15 ¹H-nmr (CDCl₃, 400MHz) δ : 1.70 (dd, 1H), 1.94 (dd, 1H), 2.65 (d, 1H), 2.79 (t, 2H), 2.92 (dd, 1H), 2.99 (t, 2H), 3.42 (m, 1H), 3.60 (m, 3H), 3.70 (s, 2H), 3.81 (dd, 2H), 4.08 (d, 1H), 4.39 (s, 1H), 6.81 (d, 1H), 7.32 (m, 5H), 8.24 (d, 1H).
LRMS: m/z (ES⁺) 336 [MH⁺]

20

Preparation 1662-Benzyl-5-(3-methoxy-azetidin-1-ylmethyl)-1,2,3,4-tetrahydro-[2,6]naphthyridine

- N,N-Diisopropylethylamine (517 mg, 4 mmol) was added to a solution of the amine hydrochloride from preparation 21 (494 mg, 4 mmol) and the aldehyde from
- 25 preparation 35 (756 mg, 3 mmol) in tetrahydrofuran (20 ml), and the solution was stirred for 10 minutes. Acetic acid (480 mg, 8 mmol) was then added, followed by sodium triacetoxyborohydride (2.12 g, 10 mmol) and the reaction mixture was stirred at room temperature for 45 minutes. 2M Hydrochloric acid (5 ml) was added, the mixture

then re-basified using 1N sodium hydroxide solution, and the mixture extracted with dichloromethane (3x50 ml). The combined organic solutions were dried over magnesium sulphate and evaporated under reduced pressure to give the final compound as a yellow oil (970mg).

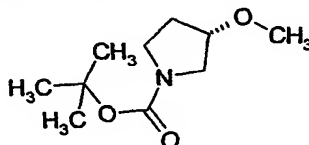
- 5 $^1\text{H-nmr}$ (CDCl_3 , 400MHz) δ : 2.78 (m, 2H), 2.86 (m, 2H), 3.03 (m, 4H), 3.22 (s, 3H), 3.58 (s, 2H), 3.67 (m, 4H), 4.03 (m, 1H), 6.78 (d, 1H), 7.25 (m, 1H), 7.34 (m, 4H), 8.23 (d, 1H).

LRMS: m/z (ES^+) 324 [MH^+]

10

Preparation 167

tert-Butyl (3S)-3-methoxy-1-pyrrolidinecarboxylate



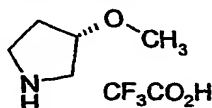
- Sodium hydride (2.2 g, 80% dispersion in mineral oil, 73.2 mmol) was added to an ice-cooled solution of (3S)-N-*tert*-butoxycarbonylpyrrolidin-3-ol (US 6180627 preparation 15 78), (12.5 g, 66.7 mmol) in tetrahydrofuran (330 ml), and the solution was stirred at room temperature for an hour. Iodomethane (14.5 g, 100 mmol) was then added and the reaction stirred for 18 hours. Water (100 ml) was added and the mixture concentrated under reduced pressure to remove the organic solvents. The solution was partitioned between water (750 ml) and ethyl acetate (750 ml) the layers separated, 20 and the organic solution dried over magnesium sulphate and evaporated under reduced pressure to give the title compound.

$^1\text{Hnmr}$ (CDCl_3 , 400MHz) δ : 1.42 (s, 9H), 1.84-2.00 (m, 2H), 3.32 (s, 3H), 3.40 (m, 4H), 3.92 (m, 1H).

25

Preparation 168

(3S)-3-Methoxypyrrolidine trifluoroacetate



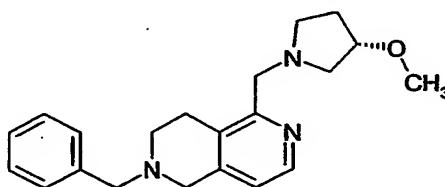
- Hydrogen chloride was bubbled through an ice-cooled solution of the protected amine from preparation 167 (23.77 g, 118 mmol) in diethyl ether (591 ml), until saturated, and 30 the solution was stirred for 1 hour at room temperature. The reaction was concentrated under reduced pressure and the residue re-suspended in diethyl ether. The mixture

was stirred for 3 hours and the ether decanted off, the residue was evaporated under reduced pressure. The product was dissolved in ethanol, trifluoroacetic acid (16 ml) added, and the solution evaporated under reduced pressure to afford the title compound.

- 5 ¹Hnmr (CDCl₃, 400MHz) δ: 2.00 (m, 1H), 2.18 (m, 1H), 3.25-3.48 (m, 7H), 4.06 (m, 1H), 8.75 (s, 1H), 9.24 (s, 1H).

Preparation 169

2-Benzyl-5-[(3S)-3-methoxypyrrolidinyl]methyl-1,2,3,4-tetrahydro[2,6]naphthyridine



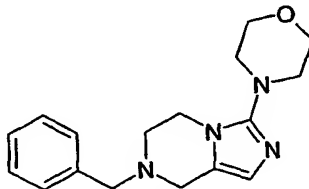
10

- A solution of the aldehyde from preparation 35 (500 mg, 2 mmol) and the pyrrolidine from preparation 168 (385 mg, 2.8 mmol) in dichloromethane (10 ml) was stirred at room temperature for 30 minutes. Sodium triacetoxyborohydride (1.05 g, 5 mmol) was added and the reaction stirred at room temperature for 18 hours. The reaction was washed with sodium bicarbonate solution, and this aqueous solution extracted with further dichloromethane (2x). The combined organic solutions were dried over magnesium sulphate and evaporated under reduced pressure. The residual oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol: 0.88 ammonia (98:2:0.2 to 90:10:1) to afford the title compound as an orange oil (290mg).
- 15
- 20

¹H-nmr (CDCl₃, 400MHz) δ: 1.82 (m, 1H), 2.13 (m, 1H), 2.60-2.82 (m, 5H), 3.00 (m, 3H), 3.27 (s, 3H), 3.60 (s, 2H), 3.70 (s, 2H), 3.80 (m, 2H), 3.97 (m, 1H), 6.81 (d, 1H), 7.22-7.40 (m, 5H), 8.24 (d, 1H).

LRMS: m/z (ES⁺) 360 [MNa⁺]

25

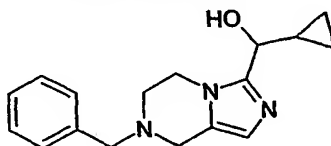
Preparation 1707-Benzyl-3-(4-morpholinyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine

A mixture of the bromide from preparation 83 (292 mg, 1 mmol) and
5 tetrakis(triphenylphosphine) palladium (0) (23 mg, 0.22 mmol) in morpholine (2 ml) was
heated under reflux for 20 hours. The cooled mixture was poured into 0.1N sodium
hydroxide solution and extracted with dichloromethane (3x50 ml). The combined
organic extracts were dried over magnesium sulphate and evaporated under reduced
pressure. The residue was purified by column chromatography on silica gel using an
10 elution gradient of ethyl acetate: methanol (100:0 to 93:7) to afford the title compound
as a yellow oil (182 mg).

¹H-nmr (CDCl₃, 400MHz) δ : 2.80 (t, 2H), 3.07 (m, 4H), 3.62 (s, 2H), 3.68 (s, 2H), 3.81
(m, 6H), 6.49 (s, 1H), 7.32 (m, 5H).

LRMS: m/z (ES⁺) 321 [MNa⁺]

15

Preparation 171(7-Benzyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazin-3-yl)(cyclopropyl)methanol

n-Butyl lithium (4.97 ml, 7.95 mmol) was added dropwise to a cooled (-78°C) solution of
20 the bromide from preparation 83 (1.60 g, 7.50 mmol) in tetrahydrofuran (16 ml), so as
to maintain the temperature below -70°C, and once addition was complete, the solution
was allowed to warm to 0°C slowly. Cyclopropanecarboxaldehyde (1.68 ml, 22.5 mmol)
was then added, the solution stirred for a further 20 minutes at 0°C, then quenched by
the addition of water (10 ml). The mixture was neutralised using 2N hydrochloric acid,
25 then extracted with ethyl acetate (3x50 ml) and methanol: dichloromethane (5:95, 3x50
ml). The combined organic solutions were dried over magnesium sulphate and
concentrated under reduced pressure. The residual oil was purified by column
chromatography on silica gel using an elution gradient of dichloromethane: methanol
(100:0 to 95:5) to afford the title compound as an orange solid (1.18 g).

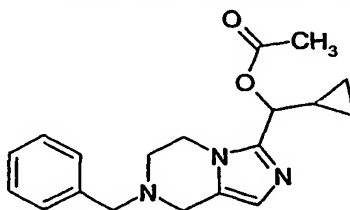
¹H-nmr (CDCl₃, 400MHz) δ: 0.40 (m, 1H), 0.46 (m, 1H), 0.62 (m, 2H), 1.42 (m, 1H), 2.17 (s, 1H), 2.83 (t, 2H), 3.65 (s, 2H), 3.69 (s, 2H), 4.07 (m, 3H), 6.67 (s, 1H), 7.25-7.35 (m, 5H).

LRMS: m/z (ES⁺) 306 [MNa⁺]

5

Preparation 172

(7-Benzyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazin-3-yl)(cyclopropyl)methyl acetate



4-Dimethylaminopyridine (40.4 mg, 0.33 mmol), triethylamine (740 μl, 5.30 mmol) and acetic anhydride (499 μl, 5.29 mmol) were added to a solution of the alcohol from preparation 171 (750 mg, 2.64 mmol) in dichloromethane (20 ml), and the reaction stirred at room temperature for 18 hours. The solution was diluted with dichloromethane (30 ml), then washed with water (10 ml), saturated sodium bicarbonate solution (10 ml), dried over magnesium sulphate and evaporated under reduced pressure. The residual brown oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol (100:0 to 95:5) to afford the title compound as an orange oil (492 mg).

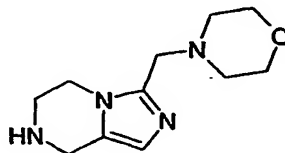
¹H-nmr (CDCl₃, 400MHz) δ: 0.37 (m, 1H), 0.50 (m, 1H), 0.65 (m, 2H), 1.72 (m, 1H), 2.07 (s, 3H), 2.82 (t, 2H), 3.64 (s, 2H), 3.68 (s, 2H), 3.94 (m, 1H), 4.02 (m, 1H), 5.21 (d, 1H), 6.75 (s, 1H), 7.31 (m, 5H).

20

LRMS: m/z (ES⁺) 348 [MNa⁺]

Preparation 173

3-Morpholin-4-ylmethyl-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazine



25

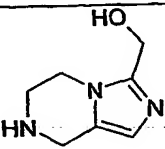
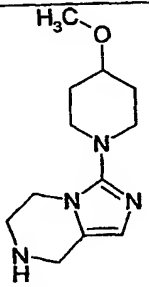
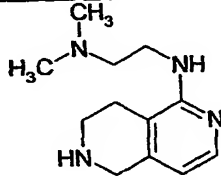
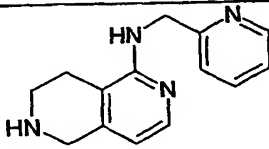
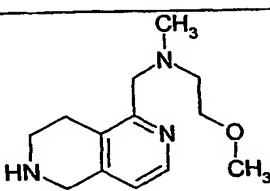
The title compound was obtained from the benzyl compound from preparation 139 (650 mg, 2.1 mmol) in 96% yield following the procedure described in preparation 109.

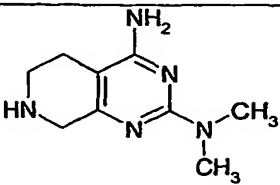
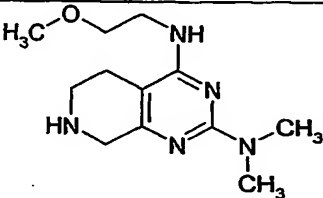
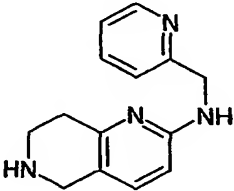
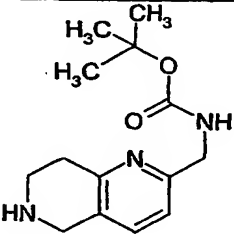
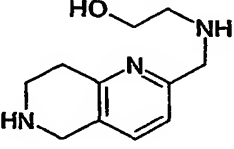
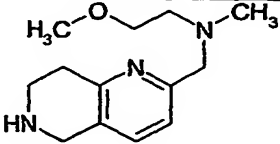
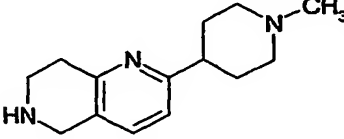
^1H -nmr (CDCl_3 , 400MHz) δ : 2.45 (m, 4H), 3.21 (t, 2H), 3.58 (m, 2H), 3.67 (m, 4H), 4.02 (t, 2H), 4.06 (s, 2H), 6.67 (s, 1H)
LRMS: m/z (ES^+) 245 [MNa^+]

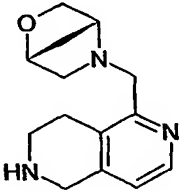
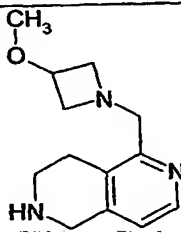
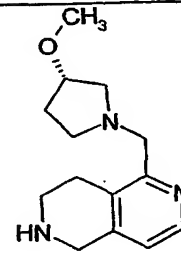
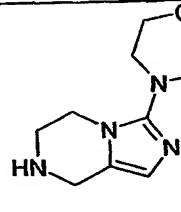
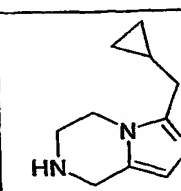
5

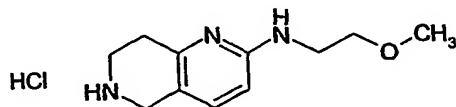
Preparations 174 to 190

The compounds of the following tabulated preparations, were prepared by a similar method to that of preparation 173 using the appropriate benzyl protected amine.

Prep	Structure	Spectroscopic Data
174		^1H -nmr (CDCl_3 , 400MHz) δ : 3.00 (s, 2H), 3.22 (t, 2H), 4.01 (m, 4H), 4.62 (s, 2H), 6.66 (s, 1H) LRMS: m/z (ES^+) 154 [MH^+]
175		^1H -nmr (CDCl_3 , 400MHz) δ : 1.65 (m, 3H), 2.03 (m, 2H), 2.90 (m, 2H), 3.15 (t, 2H), 3.26 (m, 2H), 3.33 (m, 1H), 3.39 (s, 3H), 3.74 (t, 2H), 4.01 (s, 2H), 6.50 (s, 1H) LRMS: m/z (ES^+) 237 [MH^+]
176		^1H -nmr (CDCl_3 , 400MHz) δ : 2.28 (s, 6H), 2.34 (m, 2H), 2.53 (t, 2H), 3.19 (t, 2H), 3.50 (m, 2H), 3.85 (s, 2H), 4.79 (s, 1H), 6.25 (d, 1H), 7.90 (d, 1H) LRMS: m/z (ES^+) 221 [MH^+]
177		LRMS: m/z ES^+ 241 [MH^+]
178		^1H -nmr (CDCl_3 , 400MHz) δ : 2.28 (s, 3H), 2.66 (t, 2H), 2.90 (t, 2H), 3.17 (t, 2H), 3.30 (s, 3H), 3.50 (t, 2H), 3.66 (s, 2H), 3.98 (s, 2H), 6.81 (d, 1H), 8.27 (d, 1H) LRMS: m/z ES^+ 258 [MNa^+]

Prep	Structure	Spectroscopic Data
179		¹ H-nmr (CDCl ₃ , 400MHz) δ: 2.29 (t, 2H), 3.08 (s, 6H), 3.12 (t, 2H), 3.74 (s, 2H), 4.47 (s, 2H) LRMS: m/z ES ⁺ 194 [MH ⁺]
180		¹ H-nmr (CDCl ₃ , 400MHz) δ: 2.25 (t, 2H), 3.10 (m, 8H), 3.38 (s, 3H), 3.57 (t, 2H), 3.66 (q, 2H), 3.73 (s, 2H), 4.68 (t, 1H) LRMS: m/z ES ⁺ 252 [MH ⁺]
181		¹ H-nmr (CDCl ₃ , 400MHz) δ: 2.80 (t, 2H), 3.20 (t, 2H), 3.89 (s, 2H), 4.60 (d, 2H), 5.40 (s, 1H), 6.29 (d, 1H), 7.07 (d, 1H), 7.15 (m, 1H), 7.25 (d, 1H), 7.61 (m, 1H), 8.55 (d, 1H) LRMS: m/z ES ⁺ 241.3 [MH ⁺]
182		¹ H-nmr (CDCl ₃ , 400MHz) δ: 1.47 (s, 9H), 1.60 (s, 1H), 2.91 (t, 2H), 3.20 (t, 2H), 3.97 (s, 2H), 4.35 (d, 2H), 5.41 (s, 1H), 7.02 (d, 1H), 7.26 (s, 1H) LRMS: m/z ES ⁺ 286 [MNa ⁺]
183		¹ H-nmr (DMSOd ₆ , 400MHz) δ: 2.58 (t, 2H), 2.73 (t, 2H), 3.00 (t, 2H), 3.45 (t, 2H), 3.70 (s, 2H), 3.83 (s, 2H), 7.13 (d, 1H), 7.33 (d, 1H). LRMS: m/z (ES ⁺) 208 [MH ⁺]
184		LRMS: m/z (ES ⁺) 258 [MNa ⁺]
185		¹ H-nmr (CD ₃ OD, 400MHz) δ: 2.04 (m, 4H), 2.70 (s, 3H), 2.77-2.96 (m, 3H), 3.04 (m, 2H), 3.37 (m, 4H), 4.15 (s, 2H), 7.18 (d, 1H), 7.53 (d, 1H). LRMS: m/z (ES ⁺) 232 [MH ⁺]

Prep	Structure	Spectroscopic Data
186		LRMS: m/z (ES ⁺) 258 [MNa ⁺]
187		¹ H-nmr (CDCl ₃ , 400MHz) δ: 2.78 (m, 2H), 3.03 (m, 2H), 3.17 (t, 2H), 3.21 (s, 3H), 3.63 (m, 2H), 3.72 (s, 2H), 3.96 (s, 2H), 4.02 (m, 1H), 6.80 (d, 1H), 8.24 (d, 1H). LRMS: m/z (ES ⁺) 234 [MH ⁺]
188		¹ H-nmr (CDCl ₃ , 400MHz) δ: 1.80 (m, 1H), 2.10 (m, 1H), 2.45 (s, 1H), 2.63 (dd, 1H), 2.74 (m, 2H), 2.94 (m, 2H), 2.98 (dd, 1H), 3.20 (t, 2H), 3.26 (s, 3H), 3.79 (s, 2H), 3.96 (m, 1H), 4.01 (s, 2H), 6.84 (d, 1H), 8.28 (d, 1H). LRMS: m/z (ES ⁺) 248 [MH ⁺]
189		¹ H-nmr (CDCl ₃ , 400MHz) δ: 3.08 (m, 4H), 3.18 (t, 2H), 3.77 (m, 2H), 3.80 (m, 4H), 4.02 (s, 2H), 6.52 (s, 1H). LRMS: m/z (ES ⁺) 231 [MNa ⁺]
190		¹ H-nmr (CD ₃ OD, 400MHz) δ: 0.38-0.84 (m, 4H), 1.30 (m, 1H), 3.46 (s, 2H), 3.80 (m, 2H), 4.60 (m, 4H), 7.58 (s, 1H). LRMS: m/z (ES ⁺) 178 [MH ⁺]

Preparation 191(2-Methoxy-ethyl)-(5,6,7,8-tetrahydro-[1,6]naphthyridin-2-yl)-amine hydrochloride

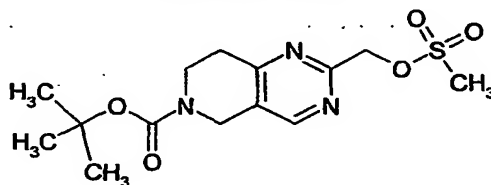
- 5 10% Palladium on activated carbon (800 mg) was added to a solution of the N-benzyl compound from preparation 148 (1.31 g, 4.4 mmol) and ammonium formate (1.39 g, 22 mmol) in methanol (50 ml). The mixture was heated under reflux for 1 hour, cooled to

room temperature and then filtered through Arbocel®. The filter cake was washed with dichloromethane/methanol (50:50, 400 ml) and the combined filtrates were evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol and ammonium hydroxide in dichloromethane as eluant (gradient from 3:0.5:97 to 10:1:90). The material isolated was azeotroped with dichloromethane and dried under vacuum. The residue was dissolved in dichloromethane (5 ml) and hydrogen chloride (1M in diethyl ether) was added. The solid formed was isolated by filtration and was dried at 60°C under vacuum to give the title compound as a pale yellow solid (832 mg).

LRMS: m/z ES⁺ 208.3 [MH⁺]

Preparation 192

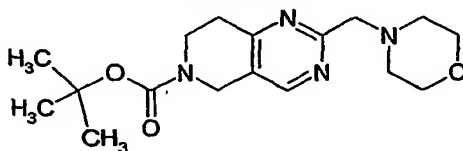
2-Methanesulfonyloxymethyl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylic acid tert-butyl ester



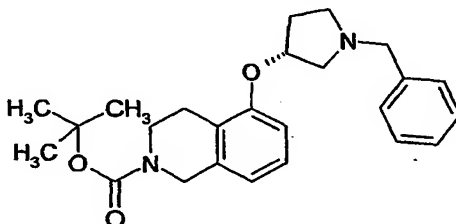
Methane sulphonyl chloride (140 μ l, 1.8 mmol) was added to a solution of the alcohol from preparation 37 (400 mg, 1.5 mmol) and triethylamine (229 μ l, 1.6 mmol) in tetrahydrofuran (10 ml) at 0°C. The mixture was warmed to room temperature and was stirred for 3 hours. The solvent was evaporated under reduced pressure and the residue was redissolved in tetrahydrofuran (10 ml) and partitioned between water (50 ml) and dichloromethane (50 ml). The organic layer was separated, dried over magnesium sulphate and evaporated under reduced pressure to give the title compound as an oil (622 mg).

¹H-nmr (CDCl₃, 400MHz) δ : 1.42 (s, 9H), 2.96 (m, 2H), 3.75 (m, 4H), 4.59 (s, 3H), 4.68 (s, 2H), 8.48 (s, 1H)

LRMS: m/z (ES⁺) 366 [MNa⁺]

Preparation 1932-Morpholin-4-ylmethyl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylic acid *tert*-butyl ester

- 5 The mesylate from preparation 192 (300 mg, 0.88 mmol) was dissolved in morpholine (5 ml) containing N,N-diisopropylethylamine (150 μ l, 0.88 mmol) and the mixture was stirred at room temperature for 16 hours. The reaction mixture was partitioned between dichloromethane (50 ml) and water (50 ml) and the organic layers were dried over magnesium sulphate and evaporated under reduced pressure. The residue was
- 10 purified by chromatography on silica gel using methanol and ammonium hydroxide in dichloromethane as eluant (gradient from 2:0.2:98 to 5:0.5:95) to give the title compound as a yellow oil (260 mg).
- ¹H-nmr (CDCl₃, 400MHz) δ : 1.50 (s, 9H), 2.59 (m, 4H), 2.96 (m, 2H), 3.74 (m, 8H), 4.58 (s, 2H), 8.45 (s, 1H)
- 15 LRMS: m/z (ES⁺) 357 [MNa⁺]

Preparation 194*tert*-Butyl 5-[[*(3R)*-1-benzylpyrrolidinyl]oxy]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate

- 20 A solution of diethylazodicarboxylate (731 mg, 4.2 mmol) in dichloromethane (5 ml) was added to an ice-cooled solution of the alcohol from preparation 22 (498 mg, 2 mmol) and triphenylphosphine (1.18 g, 4.5 mmol) in dichloromethane (35 ml), and the solution stirred for 30 minutes. (*S*)-1-Benzyl-3-pyrrolidinol (885 mg, 5 mmol) was added, the mixture allowed to warm to room temperature and the reaction stirred for a
- 25 further 72 hours. The mixture was diluted with dichloromethane (50 ml), washed with water (2x50 ml), dried over magnesium sulphate and concentrated under reduced pressure. The residual oil was purified by column chromatography on silica gel twice, using an elution gradient of cyclohexane: propan-2-ol: 0.88 ammonia (95:6:0.2 to

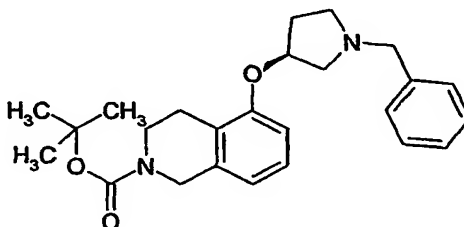
90:10:0.4). The product was azeotroped with methanol to afford the title compound as a colourless oil, 718mg.

¹H-nmr (CDCl₃, 400MHz) δ: 1.48 (s, 9H), 1.97 (m, 1H), 2.27 (m, 1H), 2.65 (m, 3H), 2.75 (t, 2H), 3.03 (dd, 1H), 3.61 (t, 2H), 3.66 (dd, 2H), 4.53 (s, 2H), 4.80 (m, 1H), 6.56 (d, 1H), 6.68 (d, 1H), 7.07 (dd, 1H), 7.22-7.37 (m, 5H).

LRMS: m/z (ES⁺) 431 [MNa⁺]

Preparation 196

tert-Butyl 5-[(3S)-1-benzylpyrrolidinyl]oxy-3,4-dihydro-2(1H)-isoquinolinecarboxylate



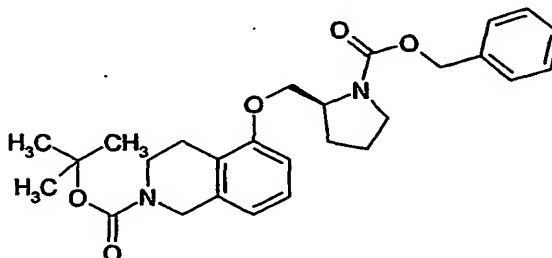
The title compound was obtained as a colourless oil in 82% yield from (R)-1-benzyl-3-pyrrolidinol and the alcohol from preparation 22, according to the method described in preparation 194.

¹H-nmr (CDCl₃, 400MHz) δ: 1.48 (s, 9H), 1.97 (m, 1H), 2.27 (m, 1H), 2.65 (m, 3H), 2.75 (t, 2H), 3.05 (dd, 1H), 3.62 (t, 2H), 3.66 (dd, 2H), 4.54 (s, 2H), 4.80 (m, 1H), 6.57 (d, 1H), 6.65 (d, 1H), 7.07 (dd, 1H), 7.22-7.37 (m, 5H).

LRMS: m/z (ES⁺) 431 [MNa⁺]

Preparation 196

tert-Butyl 5-[(2S)-1-[(benzyloxy)carbonyl]pyrrolidinyl]methoxy-3,4-dihydro-2(1H)-isoquinolinecarboxylate



The title compound was obtained as a colourless oil in 79% yield from the alcohol from preparation 22 and benzyl (2S)-2-(hydroxymethyl)-1-pyrrolidinecarboxylate (J. Chem. Soc. Perkin Trans. 1; EN; 19; 1997; 2891) (823mg, 2.53mol), following a similar

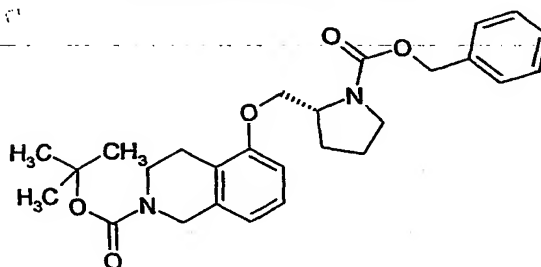
procedure to that described in preparation 195, except cyclohexane: ethyl acetate (91:9 to 75:25) was used as the elution gradient.

¹H-nmr (CDCl₃, 400MHz) δ: 1.46 (s, 9H), 1.88 (m, 1H), 2.05 (m, 3H), 2.70 (m, 2H), 3.48 (m, 2H), 3.60 (m, 3H), 4.00 (m, 2H), 4.53 (m, 2H), 5.14 (m, 2H), 6.65 (m, 2H), 7.09 (m, 1H), 7.33 (m, 5H).

LRMS: m/z (ES⁺) 490 [MNa⁺]

Preparation 197

tert-Butyl 5-((2R)-1-((benzyloxy)carbonyl)pyrrolidinyl)methoxy)-3,4-dihydro-2(1H)-isoquinolinecarboxylate



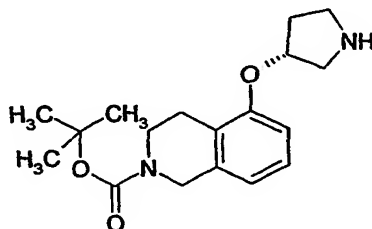
The title compound was obtained as a colourless oil in 83% yield from the alcohol from preparation 22 and benzyl (2R)-2-(hydroxymethyl)-1-pyrrolidinecarboxylate (Tet. Lett. 33; 52; 1992; 8011), following a similar procedure to that described in preparation 195.

¹H-nmr (DMSO-d₆, 400MHz) δ: 1.39 (s, 9H), 1.80 (m, 1H), 2.00 (m, 3H), 2.58 (m, 2H), 3.38 (m, 2H), 3.50 (m, 2H), 3.90-4.10 (m, 3H), 4.22 (s, 2H), 5.05 (s, 2H), 6.65-7.10 (m, 3H), 7.26 (m, 5H).

LRMS: m/z (ES⁺) 489 [MNa⁺]

Preparation 198

tert-Butyl 5-[(3R)-pyrrolidinyl]oxy]-3,4-dihydro-2(1H)-isoquinolinecarboxylate



A solution of the compound from preparation 195 (662 mg, 1.62 mmol) in methanol (60 ml) was purged with argon, then heated under reflux, and allowed to cool slightly. 10% Palladium on carbon (330 mg) and ammonium formate (204 mg, 3.25 mmol) were added, and the mixture heated at reflux for 10 minutes, then cooled rapidly to room

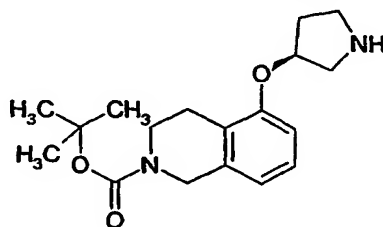
temperature. The mixture was filtered through Arbocel®, washing through with ethanol, and the combined filtrate evaporated under reduced pressure. The residual oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol: 0.88 ammonia (95:5:0.5 to 93:7:0.7) to afford the title compound as a colourless oil, 420mg.

¹H-nmr (CDCl₃, 400MHz) δ: 1.47 (s, 9H), 1.67 (s, 2H), 1.96 (m, 1H), 2.06 (m, 1H), 2.70 (t, 2H), 2.91 (m, 1H), 3.04 (dd, 1H), 3.15 (m, 1H), 3.61 (t, 2H), 4.53 (s, 2H), 4.81 (m, 1H), 6.64 (d, 1H), 6.69 (d, 1H), 7.10 (dd, 1H).

LRMS: m/z (ES⁺) 319 [MH⁺]

Preparation 199

tert-Butyl 5-[(3S)-pyrrolidinyl-3,4-dihydro-2(1H)-isoquinolinecarboxylate



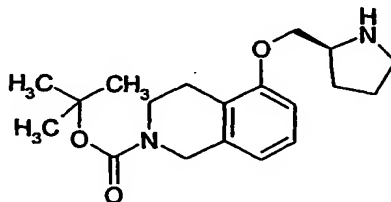
The title compound was obtained as a colourless oil in 89% yield from the compound from preparation 196, following the procedure described in preparation 198.

¹H-nmr (CDCl₃, 400MHz) δ: 1.47 (s, 9H), 1.67 (s, 2H), 1.96 (m, 1H), 2.06 (m, 1H), 2.70 (t, 2H), 2.90 (m, 1H), 3.04 (dd, 1H), 3.15 (m, 1H), 3.62 (t, 2H), 4.53 (s, 2H), 4.81 (m, 1H), 6.64 (d, 1H), 6.69 (d, 1H), 7.10 (dd, 1H).

LRMS: m/z (ES⁺) 319 [MH⁺]

Preparation 200

tert-Butyl 5-[(2S)-pyrrolidinylmethoxy]-3,4-dihydro-2(1H)-isoquinolinecarboxylate



The title compound was obtained as a colourless oil in 90% yield from the compound from preparation 196, following the procedure described in preparation 198.

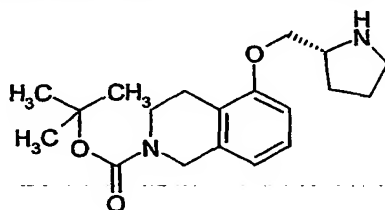
¹H-nmr (CDCl₃, 400MHz) δ: 1.47 (s, 9H), 1.60 (m, 1H), 1.66 (m, 1H), 1.80 (m, 2H), 1.95 (m, 1H), 2.75 (t, 2H), 2.94 (m, 1H), 3.02 (m, 1H), 3.52 (m, 1H), 3.61 (t, 2H), 3.90 (m, 2H), 4.54 (s, 2H), 6.70 (m, 2H), 7.10 (dd, 1H).

LRMS: m/z (ES⁺) 333 [MH⁺]

5

Preparation 201

tert-Butyl 5-[(2*R*)-pyrrolidinylmethoxy]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate



The title compound was obtained as a colourless oil in 87% yield from the compound from preparation 197, following the procedure described in preparation 198.

10

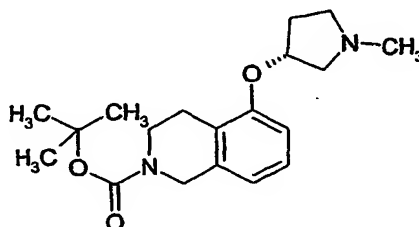
¹H-nmr (CDCl₃, 400MHz) δ: 1.47 (s, 9H), 1.60 (m, 1H), 1.66 (m, 1H), 1.80 (m, 2H), 1.95 (m, 1H), 2.75 (t, 2H), 2.94 (m, 1H), 3.02 (m, 1H), 3.52 (m, 1H), 3.61 (t, 2H), 3.90 (m, 2H), 4.54 (s, 2H), 6.69 (m, 2H), 7.10 (dd, 1H).

LRMS: m/z (ES⁺) 333 [MH⁺]

15

Preparation 202

tert-Butyl 5-[(3*R*)-1-methylpyrrolidinyl]oxy]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate



Acetic acid (156 mg, 2.6 mmol) was added dropwise to a solution of the pyrrolidine from preparation 198 (395 mg, 1.24 mmol) in tetrahydrofuran (10 ml), followed by formaldehyde (210 µl, 37%, 2.6 mmol), and the solution stirred for 20 minutes. Sodium triacetoxyborohydride (788 mg, 3.72 mmol) was added, and the reaction stirred at room temperature for 72 hours. The mixture was partitioned between dichloromethane (75 ml) and water (75 ml), and the layers separated. The aqueous phase was basified using 10% aqueous sodium carbonate solution and extracted with further dichloromethane (2x50 ml). The combined organic solutions were dried over magnesium sulphate and evaporated under reduced pressure. The residual oil was

20

25

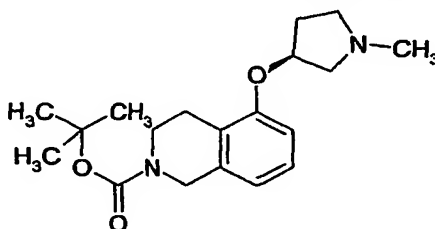
purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol: 0.88 ammonia (97:3:0.2 to 93:7:0.7), then azeotroped with methanol to afford the title compound as a pale yellow oil (378 mg).

¹H-nmr (CDCl₃, 400MHz) δ: 1.47 (s, 9H), 1.98 (m, 1H), 2.29 (m, 1H), 2.38 (s, 3H), 2.52 (m, 1H), 2.74 (m, 4H), 2.91 (m, 1H), 3.59 (dd, 2H), 4.53 (s, 2H), 4.80 (m, 1H), 6.57 (d, 1H), 6.68 (d, 1H), 7.09 (dd, 1H).

LRMS: m/z (ES⁺) 333 [MH⁺]

Preparation 203

10 *tert*-Butyl 5-[[*(3S)*-1-methylpyrrolidinyl]oxy]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate



The title compound was obtained as a pale yellow oil in 94% yield from the compound from preparation 199 and formaldehyde following the procedure described in preparation 202.

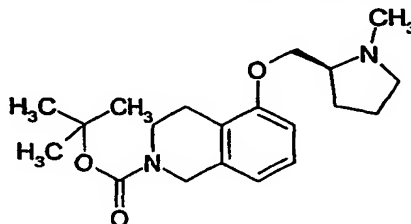
15 ¹H-nmr (CDCl₃, 400MHz) δ: 1.47 (s, 9H), 1.98 (m, 1H), 2.29 (m, 1H), 2.38 (s, 3H), 2.52 (m, 1H), 2.74 (m, 4H), 2.91 (m, 1H), 3.59 (dd, 2H), 4.53 (s, 2H), 4.80 (m, 1H), 6.57 (d, 1H), 6.68 (d, 1H), 7.09 (dd, 1H).

LRMS: m/z (ES⁺) 333 [MH⁺]

20

Preparation 204

tert-Butyl 5-[[*(2S)*-1-methylpyrrolidinyl]methoxy]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate



25 The title compound was obtained as a pale yellow oil in 94% yield from the pyrrolidine from preparation 200 and formaldehyde, following the procedure described in preparation 202.

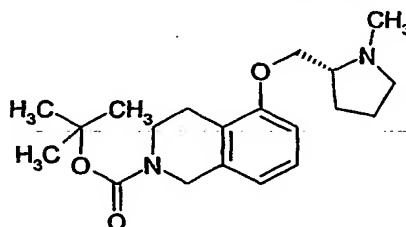
¹H-nmr (CDCl₃, 400MHz) δ: 1.47 (s, 9H), 1.68 (m, 1H), 1.79 (m, 2H), 2.03 (m, 1H), 2.30 (m, 1H), 2.48 (s, 3H), 2.66 (m, 1H), 2.74 (m, 2H), 3.09 (m, 1H), 3.60 (m, 2H), 3.84 (m, 1H), 3.98 (m, 1H), 4.54 (s, 2H), 6.68 (m, 2H), 7.10 (dd, 1H).

LRMS: m/z (ES⁺) 347 [MH⁺]

5

Preparation 204

tert-Butyl 5-[(2S)-1-methylpyrrolidinyl]methoxy-3,4-dihydro-2(1H)-isoquinolinecarboxylate



- 10 The title compound was obtained as a pale yellow oil in 90% yield from the pyrrolidine from preparation 201 and formaldehyde, following the procedure described in preparation 202.

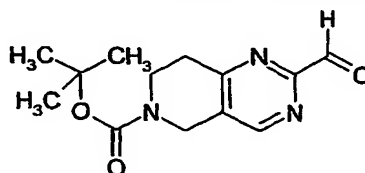
¹H-nmr (CDCl₃, 400MHz) δ: 1.47 (s, 9H), 1.68 (m, 1H), 1.79 (m, 2H), 2.03 (m, 1H), 2.30 (m, 1H), 2.48 (s, 3H), 2.66 (m, 1H), 2.74 (m, 2H), 3.09 (m, 1H), 3.60 (m, 2H), 3.84 (m, 1H), 3.98 (m, 1H), 4.54 (s, 2H), 6.68 (m, 2H), 7.10 (dd, 1H).

15

LRMS: m/z (ES⁺) 347 [MH⁺]

Preparation 205

tert-Butyl 2-formyl-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate



20

- A solution of dimethylsulphoxide (1.41 ml, 19.9 mmol) in dichloromethane (2ml) was added to a cooled (-65°C) solution of trifluoroacetic anhydride (2.08 ml, 14.9 mmol) in dichloromethane (40 ml), and the solution stirred for 30 minutes. A solution of the alcohol from preparation 37 (2.5 g, 9.96 mmol) in dichloromethane (10 ml) was added dropwise, so as to maintain the temperature below -60°C, and once addition was complete, the solution was stirred for a further 30 minutes. Triethylamine (6.94 ml, 49.8 mmol) was slowly added, the reaction stirred for a further hour at -65°C, and then poured into ethyl acetate (200 ml) and water (100 ml). The phases were separated, the

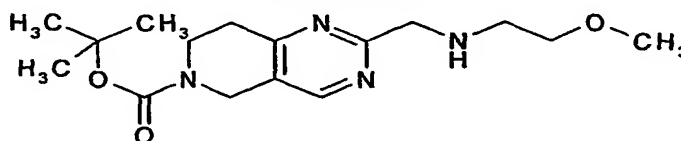
25

organic phase washed with water (150 ml), 10% aqueous citric acid solution (150 ml) and brine (150 ml), then dried over magnesium sulphate and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using ethyl acetate as eluant, to afford the title compound, 1.3g.

5 LRMS: m/z (ES^+) 286 [MNa^+]

Preparation 206

tert-Butyl 2-[[[(2-methoxyethyl)amino]methyl]-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate



10

2-Methoxyethylamine (0.21 ml, 2.45 mmol) and acetic acid (0.10 ml, 1.79 mmol) were added to a solution of the aldehyde from preparation 205 (430 mg, 1.63 mmol) in tetrahydrofuran (10 ml), and the solution stirred at room temperature for 1 hour. Sodium triacetoxyborohydride (0.87 g, 4.08 mmol) was added and the reaction stirred at room temperature for 18 hours. The mixture was concentrated under reduced pressure and the residue partitioned between 0.88 ammonia and ethyl acetate, and the layers separated. The organic phase was washed with brine, dried over magnesium sulphate and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol (98:2 to 95:5) to afford the title compound (282 mg).

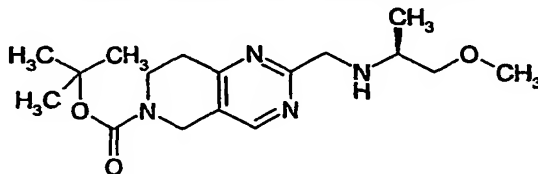
15

20

1H -nmr ($CDCl_3$, 400MHz) δ : 1.48 (s, 9H), 2.86 (t, 2H), 2.92 (t, 2H), 3.37 (s, 3H) 3.55 (t, 2H), 3.72 (t, 2H), 4.02 (s, 2H), 4.57 (s, 2H), 8.41 (s, 1H).

Preparation 207

25 *tert*-Butyl 2-[[[(1*S*)-2-methoxy-1-methylethyl]amino]methyl]-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate



The title compound was obtained, quantitatively from the aldehyde from preparation 205 and (*S*)-(+)-1-methoxy-2-propylamine, following a similar procedure to that

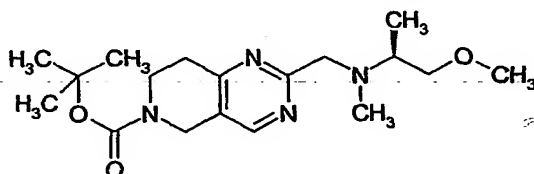
described in preparation 206, except the compound was isolated without column chromatography.

¹H-nmr (CDCl₃, 400MHz) δ: 1.07 (d, 3H), 1.45 (s, 9H), 2.94 (m, 2H), 3.35 (m, 6H), 3.74 (t, 2H), 3.96-4.10 (dd, 2H), 4.57 (s, 2H), 8.40 (s, 1H).

5 LRMS: m/z (ES⁺) 359 [MNa⁺]

Preparation 208

tert-Butyl 2-[[[(1S)-2-methoxy-1-methylethyl](methyl)amino]methyl]-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate



10

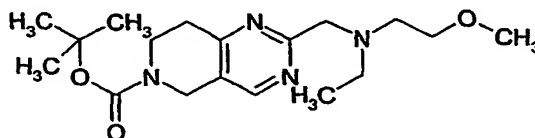
Formaldehyde (608 μl, 7.5 mmol), followed by sodium triacetoxyborohydride (2.12 g, 10 mmol) were added to a solution of the amine from preparation 207 (842 mg, 2.5 mmol) in dichloromethane (40 ml), and the reaction was stirred at room temperature for 18 hours. The mixture was partitioned between dichloromethane (100 ml) and 0.88 ammonia (100 ml), and the layers separated. The organic phase was washed with brine (100 ml), dried over sodium sulphate and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol (100:0 to 97:3) to afford the title compound, 523mg.

15

20 ¹H-nmr (CDCl₃, 400MHz) δ: 1.08 (d, 3H), 1.46 (s, 9H), 2.38 (s, 3H), 2.95 (m, 2H), 3.00 (m, 1H), 3.35 (s, 3H), 3.44 (s, 2H), 3.75 (m, 2H), 3.85 (s, 2H), 4.58 (s, 2H), 8.42 (s, 1H). LRMS: m/z (ES⁺) 373 [MNa⁺]

Preparation 209

25 tert-Butyl 2-[[ethyl(2-methoxyethyl)amino]methyl]-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate



30

Acetaldehyde (0.21 ml, 3.8 mmol) was added to a solution of the amine from preparation 206 (282 mg, 0.97 mmol) in dichloromethane (10 ml) and the solution stirred for 1 hour at room temperature. Sodium triacetoxyborohydride (1.03 g, 4.8

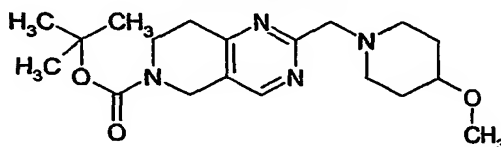
mmol) was added and the reaction was stirred at room temperature for 18 hours. The mixture was concentrated under reduced pressure and the residue partitioned between 0.88 ammonia (100 ml) and ethyl acetate (100 ml) and the layers separated. The organic phase was washed with brine (100 ml), dried over magnesium sulphate and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol (99:1 to 96:4) to afford the title compound, 90mg.

¹H-nmr (CDCl₃, 400MHz) δ: 1.08 (t, 3H), 1.48 (s, 9H), 2.72 (q, 2H), 2.81 (t, 2H), 2.91 (t, 2H), 3.33 (s, 3H), 3.54 (t, 2H), 3.75 (t, 2H), 3.92 (s, 2H), 4.57 (s, 2H), 8.44 (s, 1H).

LRMS: m/z (ES⁺) 373 [MNa⁺]

Preparation 210

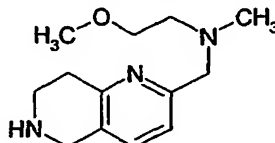
tert-Butyl 2-[(4-methoxy-1-piperidinyl)methyl]-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate



Triethylamine (305 μl, 2.19 mmol) and methanesulphonyl chloride (185 μl, 2.39 mmol) were added to a solution of the alcohol from preparation 37 (500 mg, 1.99 mmol) in dichloromethane (5 ml), and the solution stirred at room temperature for 3 hours. The mixture was evaporated under reduced pressure and the residue re-dissolved in tetrahydrofuran (5 ml) and 4-methoxypiperidine (J. Chem. Soc. 1984, (4), 737, Example 13) (1 g, 5.98 mmol) added, and the reaction mixture was stirred at room temperature for 18 hours. The mixture was partitioned between dichloromethane (30 ml) and water (30 ml), the layers separated, and the aqueous phase extracted with dichloromethane (30 ml). The combined organic solutions were dried over sodium sulphate and evaporated under reduced pressure to give a brown oil. This was purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol: 0.88 ammonia (98:2:1 to 96:4:1) to afford the title compound as a yellow gum (350 mg).

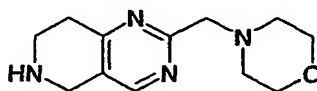
¹H-nmr (CDCl₃, 400MHz) δ: 1.49 (s, 9H), 1.68 (m, 2H), 1.89 (m, 2H), 2.28 (m, 2H), 2.81 (m, 2H), 2.95 (t, 2H), 3.21 (m, 1H), 3.32 (s, 3H), 3.73 (m, 4H), 4.57 (s, 2H), 8.45 (s, 1H).

LRMS: m/z (ES⁺) 363 [MH⁺]

Preparation 211(2-Methoxy-ethyl)-methyl-(5,6,7,8-tetrahydro-[1,6]naphthyridin-2-ylmethyl)-amine

The title compound was obtained as a pale yellow oil from the benzyl compound from preparation 156 (832 mg, 2.55 mmol) following the procedure described in preparation 109.

LRMS: m/z (ES^+) 258 [MNa^+]

Preparation 21210 2-Morpholin-4-ylmethyl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidine dihydrochloride

2 HCl

The protected amine from preparation 210 (243 mg, 0.72 mmol) was dissolved in dichloromethane (15 ml) at 0°C and hydrogen chloride gas was bubbled through the solution for 10 minutes. The solvent was removed under reduced pressure to give the title compound as a white solid (200 mg)

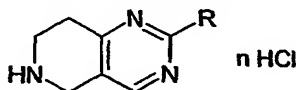
1H -nmr ($DMSO-d_6$ 400MHz) δ : 2.48 (m, 4H), 3.13 (m, 2H), 3.49 (m, 2H), 3.90 (m, 4H), 4.35 (s, 2H), 4.63 (s, 2H), 8.79 (s, 1H), 9.95 (s, 2H)

LRMS: m/z (ES^+) 235 [MH^+]

20

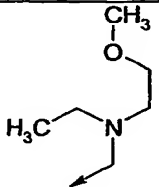
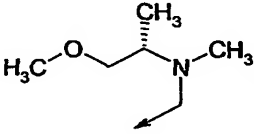
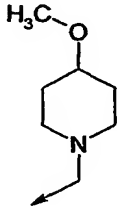
Preparations 213 to 215

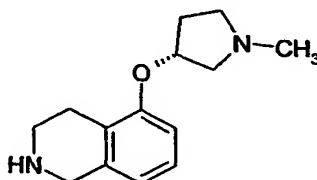
The compounds of the following tabulated preparations, of the general formula



were prepared by a similar method to that of preparation 212 using the appropriate protected amine.

25

Prep	Structure	Spectroscopic Data
213		$^1\text{H-nmr}$ (CDCl_3 , 400MHz) δ : 1.22 (t, 3H), 2.46 (m, 2H), 3.12 (t, 2H), 3.22 (s, 3H), 3.42 (m, 2H), 3.44 (m, 2H), 3.68 (t, 2H), 4.35 (s, 2H), 4.60 (s, 2H), 8.75 (s, 1H). LRMS: m/z (ES^+) 251 [MH^+]
214		$^1\text{H-nmr}$ (DMSO-d_6 , 400MHz) δ : 1.23 (m, 3H), 2.82 (s, 3H), 3.14 (t, 2H), 3.24 (m, 3H), 3.46 (m, 2H), 3.60 (m, 2H), 3.77 (m, 1H), 4.38 (s, 2H), 4.50 (m, 1H), 4.64 (m, 1H), 8.79 (s, 1H), 10.07 (m, 1H). LRMS: m/z (ES^+) 251 [MH^+]
215		$^1\text{H-nmr}$ (DMSO-d_6 , 400MHz) δ : 1.70 (m, 1H), 1.98 (m, 2H), 2.15 (m, 1H), 3.12-3.25 (m, 8H), 3.38 (m, 2H), 3.47 (m, 2H), 3.57 (m, 2H), 4.35 (s, 2H), 4.60 (s, 2H), 8.80 (s, 1H). LRMS: m/z (ES^+) 275 [MNa^+]

Preparation 2165-[[[(3R)-1-Methylpyrrolidinyl]oxy]-1,2,3,4-tetrahydroisoquinoline

- 5 Trifluoroacetic acid (5 ml) was added dropwise to a solution of the protected amine from preparation 202 (354 mg, 1.06 mmol) in dichloromethane (5 ml), and the solution then stirred at room temperature for 3.5 hours. The reaction mixture was concentrated under reduced pressure and the residue azeotroped with toluene. The crude product was purified by column chromatography on silica gel using an elution gradient of
- 10 dichloromethane: methanol: 0.88 ammonia (97:3:0.2 to 90:10:1) to afford the title compound as a colourless oil (220 mg).
- $^1\text{H-nmr}$ (CDCl_3 , 400MHz) δ : 1.98 (m, 2H), 2.28 (m, 1H), 2.38 (s, 3H), 2.52 (m, 1H), 2.65 (t, 2H), 2.69 (m, 2H), 2.93 (m, 1H), 3.11 (t, 2H), 3.96 (s, 2H), 4.80 (m, 1H), 6.55 (d, 1H), 6.60 (d, 1H), 7.04 (dd, 1H).
- 15 LRMS: m/z (ES^+) 233 [MH^+]

Preparations 217 to 219

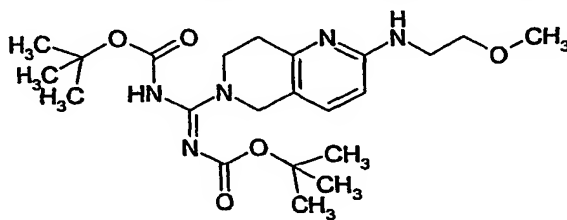
The compounds of the following tabulated preparations were prepared by a similar method to that of preparation 216 from the appropriate protected amines.

5

Prep	Structure	Spectroscopic Data
217		¹ H-nmr (CDCl ₃ , 400MHz) δ: 1.98 (m, 2H), 2.28 (m, 1H), 2.38 (s, 3H), 2.52 (m, 1H), 2.65 (t, 2H), 2.69 (m, 2H), 2.93 (m, 1H), 3.11 (t, 2H), 3.96 (s, 2H), 4.80 (m, 1H), 6.55 (d, 1H), 6.60 (d, 1H), 7.04 (dd, 1H). LRMS: m/z (ES ⁺) 233 [MH ⁺]
218		¹ H-nmr (CDCl ₃ , 400MHz) δ: 1.68 (m, 1H), 1.80 (m, 2H), 1.95 (m, 1H), 2.03 (m, 1H), 2.30 (dd, 1H), 2.50 (s, 3H), 2.67 (m, 3H), 3.11 (m, 3H), 3.84 (m, 1H), 3.96 (m, 3H), 6.63 (m, 2H), 7.06 (dd, 1H). LRMS: m/z (ES ⁺) 247 [MH ⁺]
219		¹ H-nmr (CDCl ₃ , 400MHz) δ: 1.68 (m, 1H), 1.80 (m, 2H), 2.01 (m, 1H), 2.30 (dd, 1H), 2.49 (s, 3H), 2.67 (m, 3H), 3.11 (m, 3H), 3.84 (m, 1H), 3.96 (s, 2H), 3.99 (m, 1H), 6.63 (m, 2H), 7.06 (dd, 1H). LRMS: m/z (ES ⁺) 247 [MH ⁺]

Preparation 220

{*tert*-Butoxycarbonylimino-[2-(2-methoxy-ethylamino)-7,8-dihydro-5*H*-[1,6]naphthyridin-6-yl]-methyl}-carbamic acid *tert*-butyl ester



10

Mercury (II) chloride (1.29 g, 4.78 mmol) was added to the amine from preparation 191 (0.9 g, 4.34 mmol), triethylamine (1.67 ml, 12 mmol) and 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (1.39 g, 4.78 mmol) in dichloromethane (25 ml) and the

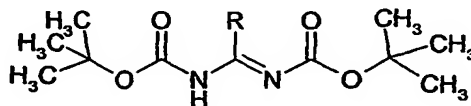
mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with dichloromethane and filtered through Arbocel® and the filtrate was evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ethyl acetate in pentane as eluant (50:50) to give the title compound as a white solid (1.5 g).

¹H-nmr (CDCl₃, 400MHz) δ: 1.50 (s, 18H), 2.93 (m, 2H), 3.36 (s, 3H), 3.48 (m, 2H), 3.55 (m, 2H), 3.80 (m, 2H), 4.57 (s, 2H), 4.68 (d, 1H), 6.24 (d, 1H), 7.11 (d, 1H), 10.08 (s, 1H)

LRMS: m/z (ES⁺) 448 [M-H]⁺

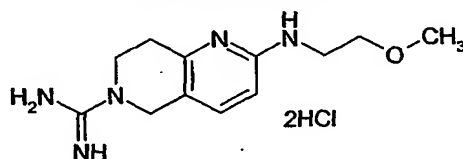
Preparations 221 to 223

The compounds of the following tabulated preparations, of the general formula:



- 15 were prepared by a similar method to that of preparation 220 using the appropriate amine.

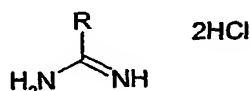
Prep	R	Spectroscopic Data
221		¹ H-nmr (CDCl ₃ , 400MHz) δ: 1.50 (s, 18H), 3.17 (t, 2H), 3.85 (t, 2H), 4.72 (s, 2H), 7.09 (m, 1H), 7.40 (d, 1H), 8.43 (d, 1H), 10.12 (s, 1H) LRMS: m/z ES ⁺ 399 [MNa ⁺]
222		¹ H-nmr (CDCl ₃ , 400MHz) δ: 1.48 (s, 18H), 2.61 (m, 2H), 3.38 (s, 3H), 3.59 (m, 2H), 3.67 (m, 2H), 3.80 (m, 2H), 4.50 (s, 1H), 4.59 (s, 2H), 6.33 (d, 1H), 7.91 (d, 1H), 10.17 (s, 1H) LRMS: m/z ES ⁺ 450 [MH ⁺]
223		¹ H-nmr (CDCl ₃ , 400MHz) δ: 1.52 (s, 18H), 2.74 (s, 2H), 3.83 (s, 2H), 4.60 (s, 2H), 4.79 (s, 2H), 5.57 (s, 1H), 6.37 (d, 1H), 7.17 (m, 1H), 7.30 (d, 1H), 7.63 (m, 1H), 7.96 (s, 1H), 8.55 (d, 1H), 10.18 (s, 1H) LRMS: m/z ES ⁺ 505 [MNa ⁺]

Preparation 2242-(2-Methoxy-ethylamino)-7,8-dihydro-5H-[1,6]naphthyridine-6-carboxamidine dihydrochloride

- 5 Hydrogen chloride gas was bubbled into a solution of the protected amidine from preparation 220 (1.5 g, 3.34 mmol) in dichloromethane for 10 minutes. The mixture was stirred at room temperature for 1 hour. The solvent was evaporated under reduced pressure to give the title compound as a white solid (1 g).
- ¹H-nmr (DMSO-d₆ 400MHz) δ: 3.04 (m, 2H), 3.27 (s, 3H), 3.52 (t, 2H), 3.63 (t, 2H), 3.74 (m, 2H), 4.51 (s, 2H), 7.01 (d, 1H), 7.60 (d, 1H), 7.79 (s, 4H)
- 10 LRMS: m/z (ES⁺) 292 [MH]⁺

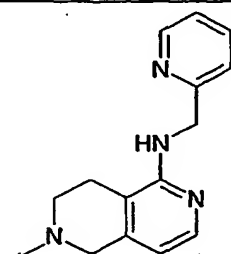
Preparations 225 to 227

- 15 The compounds of the following tabulated preparations, of the general formula:



were prepared by a similar method to that of preparation 224 using the appropriate amidine.

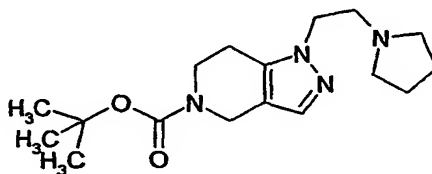
Prep	R	Spectroscopic Data
225 ^A		¹ H-nmr (DMSO-d ₆ 400MHz) δ: 3.01 (t, 2H), 3.75 (t, 2H), 4.64 (s, 2H), 7.45 (s, 5H), 7.59 (d, 1H), 8.43 (d, 1H) LRMS: m/z ES ⁺ 177 [MH] ⁺
226		¹ H-nmr (CD ₃ OD, 400MHz) δ: 2.78 (m, 2H), 3.36 (s, 3H), 3.68 (m, 4H), 3.82 (t, 2H), 4.68 (s, 2H), 6.76 (d, 1H), 6.73 (d, 1H) LRMS: m/z ES ⁺ 251 [MH] ⁺

Prep	R	Spectroscopic Data
227		$^1\text{H-nmr}$ (CD_3OD , 400MHz) δ : 2.94 (m, 2H), 3.88 (m, 2H), 4.73 (s, 2H), 5.20 (s, 2H), 6.90 (d, 1H), 7.81 (m, 1H), 7.91 (m, 1H), 8.01 (d, 1H), 8.48 (m, 1H), 8.79 (d, 1H) LRMS: m/z ES^+ 505 [MNa^+]

A Trifluoroacetic acid was used for the deprotection; the product was isolated as the ditrifluoroacetate salt

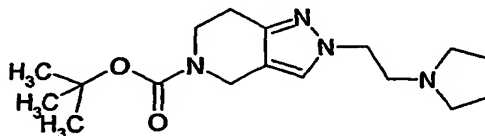
Preparation 228-A

- 5 1-(2-Pyrrolidin-1-yl-ethyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid
tert-butyl ester



Preparation 228-B

- 10 2-(2-Pyrrolidin-1-yl-ethyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine
-5-carboxylic acid *tert*-butyl ester



- 1,4,6,7-Tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid *tert*-butyl ester (1.8 g, 8.06 mmol)(EP1057814, Example 2c) was added to 1-(2-chloro-ethyl)-pyrrolidine hydrochloride (1.65 g, 9.67 mmol) and potassium carbonate (3.34 g, 24.2 mmol) in N,N-dimethylformamide (35 ml) and the mixture was heated at 65°C for 26 hours, then cooled to room temperature and stirred for 72 hours. The solvent was evaporated under reduced pressure and the residue was dissolved in 2N sodium hydroxide solution. The aqueous mixture was extracted with ethyl acetate (x2) and the combined organic layers were dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ammonium hydroxide, methanol and ethyl acetate in dichloromethane as eluant (gradient from

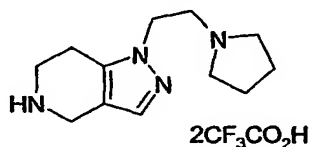
0:0:50:50 to 0:0.1:50:50 to 0.5:5:0:95) to give the title compounds from preparation 228-A and preparation 228-B as a mixture of isomers (300 mg).

LRMS: m/z ES⁺ 321 [MH⁺]

5

Preparation 229-A

1-(2-Pyrrolidin-1-yl-ethyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine
ditrifluoroacetate



Preparation 229-B

10

2-(2-Pyrrolidin-1-yl-ethyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine
ditrifluoroacetate



15

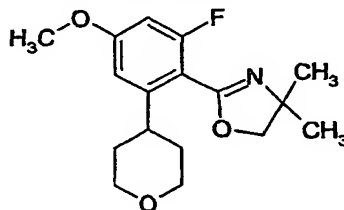
Trifluoroacetic acid (2 ml) was added to the product from preparation 228 (equimolar mixture preparation 228-A and preparation 228-B, 300 mg, 0.94 mmol) in dichloromethane under a nitrogen atmosphere. The mixture was stirred at room temperature for 1.5 hours and then the solvent was evaporated under reduced pressure. Residual trifluoroacetic acid was removed by dichloromethane azeotrope (x3) to give a mixture of the title compound from preparation 232-A containing 40% by weight the title compound from preparation 232-B as a brown gum (792 mg).

20

LRMS: m/z ES⁺ 221 [MH⁺]

Preparation 230

2-[2-Fluoro-4-methoxy-6-(tetrahydro-pyran-4-yl)-phenyl]-4,4-dimethyl-4,5-dihydro-
oxazole



25

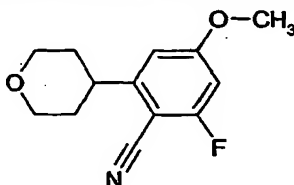
Magnesium turnings (2.4 g, 100 mmol) were added to 4-chlorotetrahydropyran (12 g, 100 mmol) in tetrahydrofuran (100ml) followed by a crystal of iodine. After initiation of the reaction the mixture reached reflux without external heating. When the reaction had subsided, the mixture was stirred at room temperature for 2 hours.

- 5 The above tetrahydropyran-4-yl magnesium chloride solution (50 ml) was added dropwise to the fluoro compound from preparation 2 (4.82 g, 20 mmol) in tetrahydrofuran (20 ml) at 0°C and the mixture was warmed to room temperature and was stirred for 2 hours. The reaction mixture was diluted with water and filtered through Arbocel®. The solution was extracted with ethyl acetate and the organic layer
10 was washed with brine and dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ethyl acetate in dichloromethane as eluant (gradient from 0:100 to 40:60) to give the title compound as a white solid (6.5 g).

- ¹H-nmr (CDCl₃, 400MHz) δ: 1.40 (s, 6H), 1.95 (m, 4H), 3.14 (m, 1H), 3.46 (m, 2H), 3.79
15 (s, 3H), 4.05 (m, 2H), 4.10 (s, 2H), 6.50 (d, 1H), 6.62 (s, 1H)
LRMS: m/z (ES⁺) 330 [MNa⁺]

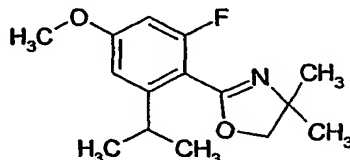
Preparation 231

2-Fluoro-4-methoxy-6-(tetrahydro-pyran-4-yl)-benzonitrile



- 20 Phosphorous oxychloride (6.14 g, 40 mmol) was added to the oxazolidine from preparation 230 (6.42 g, 21 mmol) in ethyl acetate (75 ml) and pyridine (15.8 g, 0.2 mol) and the mixture was heated under reflux for 9 hours. The reaction mixture was cooled to room temperature and was added to ice and water. The mixture was
25 extracted with ethyl acetate and the organic layer was washed with 2N hydrochloric acid (40 ml), brine (30 ml) and dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ethyl acetate in dichloromethane as eluant (gradient from 0:100 to 10:90) to give the title compound as a white solid (4.3 g).

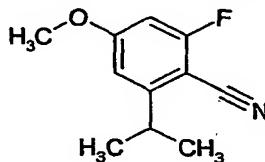
- 30 ¹H-nmr (CDCl₃, 400MHz) δ: 1.80 (m, 4H), 3.17 (m, 1H), 3.59 (m, 2H), 3.85 (s, 3H), 4.08 (m, 2H), 6.57 (d, 1H), 6.68 (s, 1H)
LRMS: m/z (ES⁺) 258 [MNa⁺]

Preparation 2322-(2-Fluoro-6-isopropyl-4-methoxy-phenyl)-4,4-dimethyl-4,5-dihydro-oxazole

Isopropyl magnesium chloride (2M in tetrahydrofuran, 0.5 ml, 1 mmol) was added
5 dropwise to the fluoro compound from preparation 2 (241 mg, 1 mmol) in
tetrahydrofuran (5 ml) at 0°C. The reaction mixture was stirred at 0°C for 15 minutes
and then was stirred at room temperature for 16 hours. The reaction mixture was
added to water and the solution was extracted with dichloromethane (3x30 ml). The
combined organic solutions were dried over magnesium sulphate and evaporated
10 under reduced pressure. The residue was purified by chromatography on silica gel
using ethyl acetate in hexane as eluant (gradient from 0:100 to 30:70) to give the title
compound as a colourless oil (110 mg).

¹H-nmr (CDCl₃, 400MHz) δ: 1.21 (d, 6H), 1.39 (s, 6H), 3.28 (m, 1H), 3.80 (s, 3H), 4.08
(s, 2H), 6.47 (d, 1H), 6.65 (s, 1H)

15 LRMS: m/z (ES⁺) 266 [MH⁺]

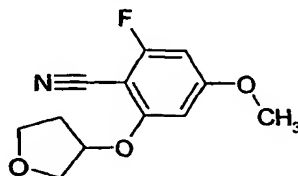
Preparation 2332-Fluoro-6-isopropyl-4-methoxy-benzonitrile

20 The title compound was obtained from the compound from preparation 232 (2.43 g,
9.17 mmol) in 95% yield following the procedure described in preparation 231.

¹H-nmr (CDCl₃, 400MHz) δ: 1.30 (d, 6H), 3.31 (m, 1H), 6.83 (s, 3H), 6.55 (d, 1H), 6.67
(s, 1H)

LRMS: m/z (ES⁺) 216 [MNa⁺]

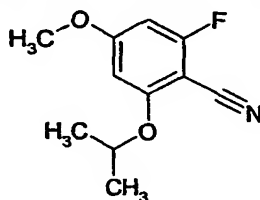
25

Preparation 2342-Fluoro-4-methoxy-6-(tetrahydro-furan-3-yloxy)-benzonitrile

Sodium hydride (60% in mineral oil, 0.83 g, 21 mmol) was added portionwise to 3-hydroxytetrahydrofuran (1.82 g, 21 mmol) in tetrahydrofuran (40 ml) at 0°C under a nitrogen atmosphere. The suspension was warmed to room temperature and was stirred for 1 hour. The mixture formed was added over 30 minutes to 2,6-difluoro-4-methoxy-benzonitrile (Mol. Cryst. Liq. Cryst. 1989, 172) (3.5 g, 21 mmol) in tetrahydrofuran (50 ml) and the resulting solution was held at room temperature for 16 hours. Water (75 ml) was added and the aqueous mixture was extracted with ethyl acetate (3x200 ml) The combined organic solutions were dried over magnesium sulphate and evaporated under reduced pressure. The material obtained was dried under vacuum to give the title compound as a brown solid (5.1 g).

¹H-nmr (CDCl₃, 400MHz) δ: 2.20 (m, 2H), 3.84 (s, 3H), 4.00 (m, 4H), 4.95 (m, 1H), 6.18 (s, 1H), 6.32 (d, 1H)

LRMS: *m/z* ES⁺ 260 [MNa⁺]

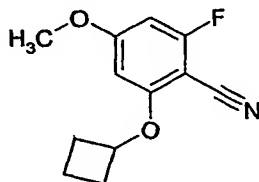
Preparation 2352-Fluoro-6-isopropoxy-4-methoxy-benzonitrile

20

The title compound was obtained from 2,6-difluoro-4-methoxy-benzonitrile (Mol. Cryst. Liq. Cryst. 1989, 172) in 49% yield following the procedure described in preparation 234.

¹H-nmr (CDCl₃, 400MHz) δ: 1.40 (d, 6H), 3.85 (s, 3H), 4.59 (m, 1H), 6.24 (m, 2H)

25 LRMS: *m/z* ES⁺ 210 [MH⁺]

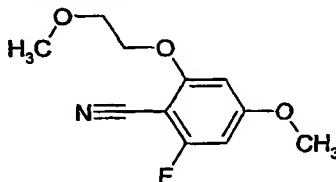
Preparation 2362-Cyclobutoxy-6-fluoro-4-methoxy-benzonitrile

The title compound was obtained from 2,6-difluoro-4-methoxy-benzonitrile (Mol. Cryst. Liq. Cryst. 1989, 172) in 80% yield following the procedure described in preparation 234.

^1H -nmr (CDCl_3 , 400MHz) δ : 1.68 (m, 1H), 1.88 (m, 1H), 2.23 (m, 2H), 2.42 (m, 2H), 3.78 (s, 3H), 4.65 (m, 1H), 6.06 (s, 1H), 6.24 (d, 1H)

LRMS: m/z (ES^+) 244 [MNa^+]

10

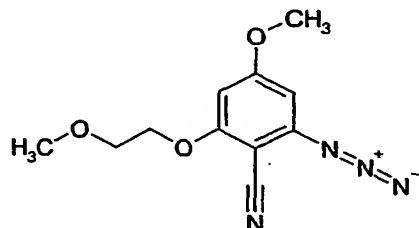
Preparation 2372-Fluoro-4-methoxy-6-(2-methoxy-ethoxy)-benzonitrile

Sodium hydride (60% in mineral oil, 0.88 g, 22 mmol) was added to 2-methoxyethanol (1.84 g, 24 mmol) in tetrahydrofuran (20 ml) and the mixture was stirred at room temperature for 20 minutes. 2,6-Difluoro-4-methoxy-benzonitrile (Mol. Cryst. Liq. Cryst. 1989, 172) (3.38 g, 20 mmol) was added and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into water and the solution was extracted with dichloromethane (3x50 ml). The combined organic solutions were dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 0:100 to 3:97) to give the title compound (3.8 g).

^1H -nmr (CDCl_3 , 400MHz) δ : 3.46 (s, 3H), 3.78 (t, 2H), 3.81 (s, 3H), 4.20 (t, 2H), 6.30 (m, 2H)

LRMS: m/z ES^+ 248 [MNa^+]

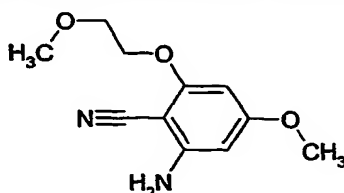
25

Preparation 2382-Azido-4-methoxy-6-(2-methoxy-ethoxy)-benzonitrile

The fluoro compound from preparation 237 (3.6 g, 16 mmol) was added to sodium azide (1.56 g, 24 mmol) in N,N-dimethylformamide (25 ml) and the mixture was heated at 100°C for 8 hours. The reaction mixture was cooled to room temperature and was added to water. The aqueous mixture was extracted with dichloromethane (3x60 ml) and the combined organic solutions were dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ethyl acetate in dichloromethane as eluant (gradient from 0:100 to 20:80) to give the title compound (3.51 g).

¹H-nmr (CDCl₃, 400MHz) δ: 3.47 (s, 3H), 3.79 (t, 2H), 3.86 (s, 3H), 4.20 (t, 2H), 6.30 (2xs, 2H)

LRMS: *m/z* ES⁺ 248 [MNa⁺]

Preparation 2392-Amino-4-methoxy-6-(2-methoxy-ethoxy)-benzonitrile

The azide from preparation 238 (3.50 g, 14.1 mmol) was suspended in methanol (100 ml) and magnesium turnings (1.68 g, 70 mmol) were added. The mixture was stirred for 18 hours and then 1N citric acid was added. The aqueous mixture was extracted with dichloromethane (3x100 ml) and the combined organic solutions were dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 0:100 to 5:95). The material obtained was triturated with diethyl ether to give the title compound as a white solid (1.78 g).

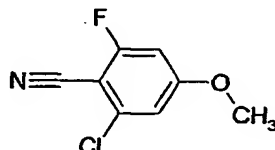
¹H-nmr (CDCl₃, 400MHz) δ: 3.43 (s, 3H), 3.77 (m, 5H), 4.12 (t, 2H), 4.37 (s, 2H), 5.82 (s, 1H), 5.86 (s, 1H)

LRMS: *m/z* ES⁺ 245 [MNa⁺]

5

Preparation 240

2-Chloro-6-fluoro-4-methoxy-benzonitrile



10 A solution of sodium nitrite (3.73 g, 54 mmol) in water (20 ml) was added to the amino compound from preparation 291 (8.3 g, 50 mmol) in concentrated hydrochloric acid at -10°C at a rate that maintained the temperature below -5°C. The solution was stirred at -5°C for 1 hour and then was added dropwise to copper (I) chloride (9.9 g, 0.1 mol) in water (100 ml) at -10°C. The reaction mixture was warmed to room temperature and was stirred for 16 hours and then the aqueous mixture was extracted with dichloromethane (x3). The combined organic solutions were washed with 1M sodium

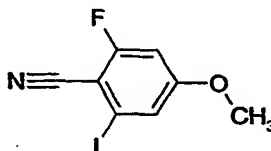
15 hydroxide solution (2x250 ml) and water (250 ml) then dried over sodium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using cyclohexane in dichloromethane as eluant (25:75) to give the title compound as a white solid (6.5 g).

¹H-nmr (CDCl₃, 400MHz) δ: 3.87 (s, 3H), 6.65 (dd, 1H), 6.85 (d, 1H)

20 LRMS: *m/z* (ES⁺) 208 [MNa⁺]

Preparation 241

2-Fluoro-6-iodo-4-methoxy-benzonitrile



25 Sodium nitrite (227 mg, 3.3 mmol) in water (1 ml) was added dropwise to the amino compound from preparation 291 (500 mg, 3 mmol) in concentrated hydrochloric acid (10 ml) at -10°C. The mixture was stirred at -10°C for 1 hour and then was added dropwise to potassium iodide (996 mg, 6 mmol) in water (5 ml) at -10°C. The reaction mixture was warmed to room temperature and was stirred for 72 hours. The reaction

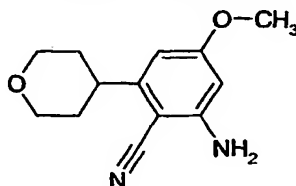
mixture was extracted with dichloromethane (3x50 ml) and the combined organic extracts were washed with 10% sodium metabisulphite solution (100 ml), 1M sodium hydroxide solution (100 ml) and water (100 ml) The organic solution was dried over magnesium sulphate and evaporated under reduced pressure to give the title compound as a yellow solid (751 mg).

¹H-nmr (DMSO-d₆ 400MHz) δ: 3.85 (s, 3H), 7.15 (d, 1H), 7.45 (s, 1H)

LRMS: m/z ES⁺ 300 [MNa⁺]

Preparation 242

2-Amino-4-methoxy-6-(tetrahydro-pyran-4-yl)-benzonitrile



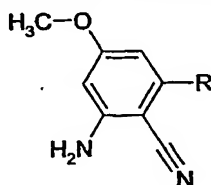
Ammonia gas was bubbled into dimethylsulphoxide (30 ml) for 20 minutes and the fluoro compound from preparation 231 (4.2 g, 17.9 mmol) was added and the mixture was heated at 150°C for 18 hours. The reaction mixture was cooled to room temperature and was added to ethyl acetate (200 ml). The organic solution was washed with water (100 ml), 1N citric acid (40 ml) and brine (40 ml), then dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ethyl acetate in dichloromethane as eluant (gradient from 0:100 to 25:75) to give the title compound as a white solid (1.64 g).

¹H-nmr (CDCl₃, 400MHz) δ: 1.79 (m, 4H), 3.06 (m, 1H), 3.57 (m, 1H), 3.79 (s, 3H), 4.06 (m, 2H), 4.39 (s, 2H), 6.08 (d, 1H), 6.23 (s, 1H)

LRMS: m/z (ES⁺) 255 [MNa⁺]

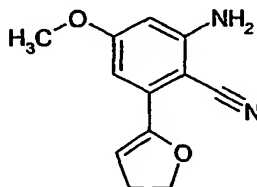
Preparations 243 to 248

The compounds of the following tabulated preparations, of the general formula:



- 5 were prepared by a similar method to that of preparation 242 from the appropriate fluoro compound.

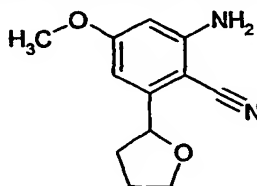
Prep	R	Spectroscopic Data
243		¹ H-nmr (CDCl ₃ , 400MHz) δ: 1.28 (d, 6H), 3.19 (m, 1H), 3.75 (s, 3H), 4.35 (s, 2H), 6.06 (s, 1H), 6.24 (s, 1H) LRMS: m/z (ES ⁺) 213 [MNa ⁺]
244		¹ H-nmr (CDCl ₃ , 400MHz) δ: 2.18 (m, 2H), 3.75 (s, 3H), 3.98 (m, 4H), 4.38 (s, 2H), 4.90 (m, 1H), 5.72 (s, 1H), 5.81 (s, 1H) LRMS: m/z ES ⁺ 257 [MNa ⁺]
245		¹ H-nmr (CDCl ₃ , 400MHz) δ: 1.36 (d, 6H), 3.77 (s, 3H), 4.35 (s, 2H), 4.53 (m, 1H), 5.81 (m, 2H) LRMS: m/z ES ⁺ 229 [MNa ⁺]
246	Cl	¹ H-nmr (CDCl ₃ , 400MHz) δ: 3.78 (s, 3H), 4.50 (s, 2H), 6.09 (s, 1H), 6.39 (s, 1H) LRMS: m/z (ES ⁺) 181, 183 [M ⁺]
247		¹ H-nmr (CDCl ₃ , 400MHz) δ: 1.67 (m, 1H), 1.87 (m, 1H), 2.21 (m, 2H), 2.40 (m, 2H), 3.74 (s, 3H), 4.35 (s, 2H), 4.61 (m, 1H), 4.65 (s, 1H), 5.79 (s, 1H) LRMS: m/z (ES ⁺) 241 [MNa ⁺]
248	I	¹ H-nmr (CDCl ₃ , 400MHz) δ: 3.77 (s, 3H), 4.43 (s, 2H), 6.15 (s, 1H), 6.80 (s, 1H) LRMS: m/z ES ⁺ 297 [MNa ⁺]

Preparation 2492-Amino-6-(4,5-dihydro-furan-2-yl)-4-methoxy-benzonitrile

The iodo compound from preparation 248 (2.1g, 7.7 mmol) in 1,4-dioxane (15 ml) was added to a solution of tris-(dibenzylideneacetone)dipalladium(0) (174 mg, 0.19 mmol) and tri-furan-2-yl-phosphine (88.2 mg, 0.38 mmol) in 1,4-dioxane (15 ml) under an argon atmosphere. Tributyl-(4,5-dihydro-furan-2-yl)-stannane (5.5 g, 15.3 mmol) was added and the mixture was heated under reflux for 1.25 hours and then was cooled to room temperature. 1M Potassium fluoride solution (22 ml) was added and the mixture was stirred at room temperature for 30 minutes. The mixture was filtered and the filter cake was washed with ethyl acetate (75 ml). The filtrate was diluted with water and extracted with ethyl acetate (2x75 ml), the combined organic solutions were dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ethyl acetate in cyclohexane as eluant (10:90). The material obtained was dissolved in acetonitrile and was washed with hexane (2x60 ml). The acetonitrile layer was separated and evaporated under reduced pressure to give the title compound as a yellow solid (1.34 g).

¹H-nmr (DMSOd₆, 400MHz) δ: 2.78 (m, 2H), 3.72 (s, 3H), 4.37 (t, 2H), 5.76 (t, 1H), 5.84 (s, 2H), 6.33 (s, 1H), 6.39 (s, 1H)

LRMS: *m/z* ES⁺ 239 [MNa⁺]

Preparation 2502-Amino-4-methoxy-6-(tetrahydro-furan-2-yl)-benzonitrile

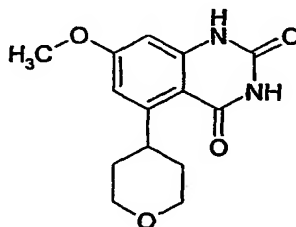
The dihydrofuran from preparation 249 (1.29 g, 5.96 mmol) was dissolved in methanol (125 ml) and the solution was purged with argon. 10% Palladium on active carbon (1.29 g) and ammonium formate (12.9 g, 0.2 mol) were added and the mixture was heated under reflux for 15 minutes. The mixture was cooled and filtered through

Arbocel®. The filter cake was washed with ethanol. The combined organic solutions were evaporated under reduced pressure and the residue was partitioned between ethyl acetate (200 ml) and water (200 ml). Sodium carbonate was added to give pH10 and the phases were separated. The aqueous phase was extracted with ethyl acetate (2x50 ml) and the combined organic solutions were dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ethyl acetate in cyclohexane as eluant (10:90) and the material obtained was co-evaporated with diethyl ether to give the title compound as a white solid (473 mg).

¹H-nmr (CDCl₃, 400MHz) δ: 1.75 (m, 1H), 2.00 (m, 2H), 2.51 (m, 1H), 3.79 (s, 3), 3.94 (q, 1H), 4.13 (q, 1H), 4.35 (s, 2H), 5.02 (t, 1H), 6.10 (s, 1H), 6.48 (s, 1H)
LRMS: *m/z* ES⁺ 241 [MNa⁺]

Preparation 251

7-Methoxy-5-(tetrahydro-pyran-4-yl)-1H-quinazoline-2,4-dione



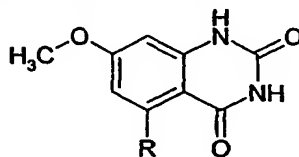
1,8-Diazabicyclo[5.4.0]undec-7-ene (3 ml) was added to the nitrile from preparation 242 (1.6 g, 6.9 mmol) in N,N-dimethylformamide (15 ml) and the solution was cooled to -78°C and solid carbon dioxide (6 g) was added. The mixture was heated at 140°C and 600 psi for 18 hours and then cooled to room temperature and added to water. The aqueous solution was acidified with 2N hydrochloric acid and the solid formed was isolated by filtration. The filter cake was washed with water and dried at 100°C under vacuum to give the title compound as a white solid (1.81 g).

¹H-nmr (DMSO-d₆, 400MHz) δ: 1.61 (m, 4H), 3.40 (m, 2H), 3.79 (s, 3H), 3.92 (m, 1H), 6.52 (d, 1H), 6.60 (s, 1H)

LRMS: *m/z* (ES⁺) 299 [MNa⁺]

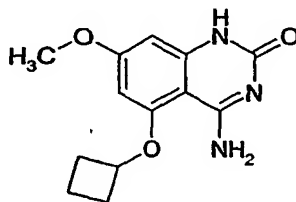
Preparations 252 to 257

The compounds of the following tabulated preparations of the general formula:



- 5 were prepared by a similar method to that of preparation 251 from the appropriate nitrile compound.

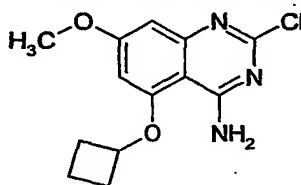
Prep	R	Spectroscopic Data
252		¹ H-nmr (DMSO-d ₆ 400MHz) δ: 1.13 (d, 6H), 3.79 (s, 3H), 4.49 (m, 1H), 6.52 (d, 1H), 6.61 (d, 1H) LRMS: m/z (ES ⁺) 491 [2MNa ⁺]
253		¹ H-nmr (DMSO-d ₆ 400MHz) δ: 1.99 (m, 1H), 2.15 (m, 1H), 3.80 (m, 7H), 5.01 (m, 1H), 6.08 (s, 1H), 6.23 (s, 1H) LRMS: m/z ES ⁺ 301 [MNa ⁺]
254		¹ H-nmr (DMSO-d ₆ 400MHz) δ: 3.35 (s, 3H), 3.66 (t, 2H), 3.78 (s, 3H), 4.10 (m, 2H), 6.24 (m, 2H) LRMS: m/z (ES ⁺) 555 [2MNa ⁺]
255		¹ H-nmr (DMSO-d ₆ 400MHz) δ: 1.28 (d, 6H), 3.78 (s, 3H), 4.59 (m, 1H), 6.22 (s, 2H) LRMS: m/z ES ⁺ 273 [MNa ⁺]
256	Cl	¹ H-nmr (DMSO-d ₆ 400MHz) δ: 3.80 (s, 3H), 6.59 (s, 1H), 6.79 (s, 1H) LRMS: m/z (ES ⁺) 225, 227 [M ⁺ H]
257		¹ H-nmr (DMSO-d ₆ 400MHz) δ: 1.47 (m, 1H), 1.73 (m, 1H), 1.83 (m, 1H), 2.45 (m, 1H), 3.80 (m, 4H), 4.03 (m, 1H), 5.75 (t, 1H), 6.52 (s, 1H), 6.80 (s, 1H), 10.98 (2xs, 2H) LRMS: m/z ES ⁺ 262 [MNa ⁺]

Preparation 2584-Amino-5-cyclobutoxy-7-methoxy-1H-quinazolin-2-one

Trifluoroacetic acid (6.7 ml, 84 mmol) was added to a suspension of sodium cyanate
5 (5.4 g, 84 mmol) in dichloromethane (120 ml) at 0°C under a nitrogen atmosphere.
The mixture was warmed to room temperature and was stirred for 45 minutes. The
amino nitrile from preparation 247 (7.3 g, 33 mmol) was added in dichloromethane (100
ml) and the reaction mixture was stirred at room temperature for 4 hours. The solid
formed was isolated by filtration and the filter cake was washed with water and then
10 with diethyl ether. The residue was re-suspended in water and was stirred for 2 hours
and then isolated by filtration. The filter cake was washed with water and diethyl ether
then dried under vacuum to give the title compound as a white solid (5.9 g).

¹H-nmr (DMSO-d₆ 400MHz) δ: 1.59 (m, 1H), 1.78 (m, 1H), 2.00 (m, 2H), 3.74 (s, 3H),
4.77 (m, 1H), 6.05 (s, 1H), 6.21 (s, 2H), 7.34 (s, 1H), 8.20 (s, 1H)

15 LRMS: *m/z* ES⁺ 284 [MNa⁺]

Preparation 2592-Chloro-5-cyclobutoxy-7-methoxy-quinazolin-4-ylamine

20 The quinazolinone from preparation 258 (3 g, 11 mmol) was suspended in acetonitrile
(30 ml) and tetraethylammonium chloride (2.1 g, 11 mmol), N,N-dimethylaniline (1.46
ml, 11 mmol) and phosphorous oxychloride (5.35 ml, 57 mmol) were added. The
mixture was heated to 75°C over 20 minutes and then was cooled to room
temperature. The mixture was added to ice and then saturated sodium carbonate
25 solution was added to give pH 9. The solution was extracted with dichloromethane
containing 5% methanol (x3). The combined organic solutions were dried over sodium
sulphate and evaporated under reduced pressure. The residue was purified by

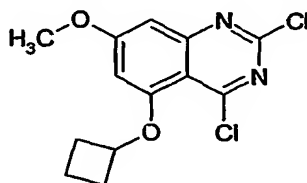
chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 0:100 to 10:90) to give the title compound as a white solid (1.11 g).

^1H -nmr (CDCl_3 , 400MHz) δ : 1.78 (m, 1H), 1.96 (m, 1H), 2.23 (m, 2H), 2.56 (m, 2H), 3.83 (s, 3H), 4.74 (m, 1H), 5.90 (s, 1H), 6.20 (s, 1H), 6.70 (s, 1H), 7.52 (s, 1H)

5 LRMS: m/z ES^+ 280, 282 [MH^+]

Preparation 260

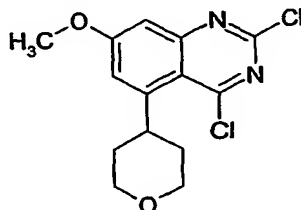
2,4-Dichloro-5-cyclobutoxy-7-methoxy-quinazoline



10 Antimony (III) chloride (4 g, 17.4 mmol) was added to a suspension of the amino compound from preparation 259 (2.43 g, 8.7 mmol) in dichloromethane (50 ml) and acetonitrile (50 ml) and the mixture was cooled to -10°C and *tert*-butyl nitrite (3.6 ml, 30.4 mmol) was added dropwise. The mixture was stirred at -10°C for 1 hour, at room temperature for 1.5 hours and under reflux for 16 hours. The reaction mixture was
15 cooled to room temperature and was added to ice. The mixture was filtered and the phases were separated. The aqueous phase was extracted with dichloromethane (x2) and the combined organic solutions were dried over sodium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ethyl acetate in pentane as eluant (gradient from 5:95 to 15:85) to give the title
20 compound as an off white solid (200 mg).

^1H -nmr (CDCl_3 , 400MHz) δ : 1.79 (m, 1H), 1.98 (m, 1H), 2.33 (m, 3H), 2.55 (m, 2H), 3.93 (m, 1H), 6.40 (s, 1H), 6.88 (s, 1H)

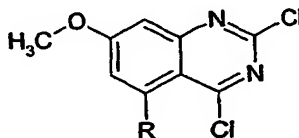
LRMS: m/z ES^+ 321, 323 [MNa^+]

Preparation 2612,4-Dichloro-7-methoxy-5-(tetrahydro-pyran-4-yl)-quinazoline

- The quinazolinedione from preparation 251 (1.76 g) was suspended in phosphorous
5 oxychloride (20 ml) and N,N-diisopropylethylamine (1.98 g, 15.3 mmol) was added
dropwise. The mixture was heated at 90°C for 2 hours and then was heated under
reflux for 3 hours. The reaction mixture was cooled to room temperature and
evaporated under reduced pressure. The residue was partitioned between water and
ethyl acetate, the organic phase separated and washed with water and brine, then
10 dried over magnesium sulphate and evaporated under reduced pressure. The residue
was purified by chromatography on silica gel using ethyl acetate in dichloromethane as
eluant (gradient from 0:100 to 25:75) to give the title compound as a white solid (1.2 g).
¹H-nmr (CDCl₃, 400MHz) δ: 1.88 (m, 4H), 3.62 (m, 2H), 3.97 (s, 3H), 4.12 (m, 2H), 4.35
(m, 1H), 7.19 (dd, 1H), 7.22 (d, 1H)
15 LRMS: m/z (ES⁺) 335, 337 [MNa⁺]

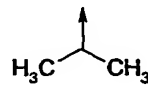
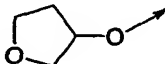
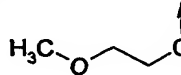
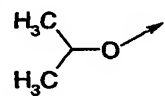
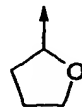
Preparations 262 to 267

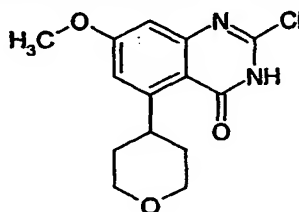
The compounds of the following tabulated preparations of the general formula:



20

were prepared by a similar method to that of preparation 261 using the appropriate
quinazolinedione compound.

Prep	R	Spectroscopic Data
262		¹ H-nmr (CDCl ₃ , 400MHz) δ: 1.38 (d, 6H), 3.95 (s, 3H), 4.52 (m, 1H), 7.15 (s, 1H), 7.29 (d, 1H) LRMS: m/z (ES ⁺) 271, 273 [MNa ⁺]
263		¹ H-nmr (DMSO-d ₆ , 400MHz) δ: 2.10 (m, 1H), 2.28 (m, 1H), 3.90 (m, 7H), 5.29 (m, 1H), 6.80 (s, 1H), 6.99 (s, 1H) LRMS: m/z ES ⁺ 337, 339 [MNa ⁺]
264		¹ H-nmr (CDCl ₃ , 400MHz) δ: 3.48 (s, 3H), 3.88 (s, 2H), 3.94 (s, 3H), 4.23 (s, 2H), 6.59 (s, 1H), 6.90 (s, 1H) LRMS: m/z ES ⁺ 303, 305 [MH ⁺]
265		¹ H-nmr (CDCl ₃ , 400MHz) δ: 1.50 (d, 6H), 3.93 (s, 3H), 4.71 (m, 1H), 6.55 (s, 1H), 6.87 (s, 1H) LRMS: m/z ES ⁺ 197 [MH ⁺]
266	Cl	¹ H-nmr (CDCl ₃ , 400MHz) δ: 3.95 (s, 3H), 7.22 (s, 1H), 7.27 (s, 1H)
267		¹ H-nmr (CDCl ₃ , 400MHz) δ: 1.91 (m, 3H), 2.68 (m, 1H), 3.99 (m, 4H), 4.21 (m, 1H), 6.18 (m, 1H), 7.19 (d, 1H), 7.64 (d, 1H) LRMS: m/z ES ⁺ 321 [MNa ⁺]

Preparation 2682-Chloro-7-methoxy-5-(tetrahydro-pyran-4-yl)-3H-quinazolin-4-one

- 5 The dichloride from preparation 261 (1.17 g, 3.74 mmol) was added to 1,4-dioxane (20 ml) and 1M sodium hydroxide solution (20 ml) and the mixture was stirred at room temperature for 2 hours. The reaction mixture was acidified with 2M hydrochloric acid (15 ml) and was extracted with methanol in dichloromethane (10:90, 5x 50 ml). The combined organic solutions were dried over magnesium sulphate and evaporated
- 10 under reduced pressure. The residue was triturated with diethyl ether to give the title compound as a white solid (0.98 g).

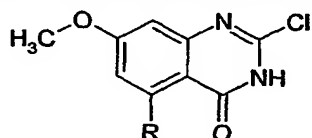
^1H -nmr (DMSO- d_6 400MHz) δ : 1.64 (m, 4H), 3.42 (m, 2H), 3.85 (s, 3H), 4.12 (m, 2H), 4.35 (m, 1H), 6.93 (s, 2H)

LRMS: m/z (ES^-) 293, 295 [M-H]

5

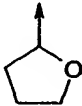
Preparations 269 to 275

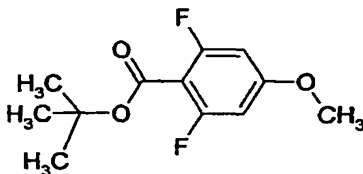
The compounds of the following tabulated preparations of the general formula:



10 were prepared by a similar method to that of preparation 268 from the appropriate dichloro compound.

Prep	R	Spectroscopic Data
269		^1H -nmr (CDCl_3 , 400MHz) δ : 1.29 (d, 6H), 3.92 (s, 3H), 4.55 (m, 1H), 6.93 (d, 1H), 7.01 (s, 1H) LRMS: m/z (ES^+) 275, 277 [MNa^+]
270		^1H -nmr (DMSO- d_6 400MHz) δ : 2.00 (m, 1H), 2.19 (m, 1H), 3.80 (m, 7H), 5.08 (m, 1H), 6.52 (s, 1H), 6.62 (s, 1H) LRMS: m/z ES^+ 319, 321 [MNa^+]
271		^1H -nmr (DMSO- d_6 400MHz) δ : 3.33 (s, 3H), 3.68 (t, 2H), 3.83 (s, 3H), 4.15 (t, 2H), 6.56 (d, 1H), 6.60 (d, 1H) LRMS: m/z ES^+ 307, 309 [MH^+]
272		^1H -nmr (DMSO- d_6 400MHz) δ : 1.30 (d, 6H), 3.83 (s, 3H), 4.66 (m, 1H), 6.55 (s, 1H), 6.60 (s, 1H) LRMS: m/z ES^+ 291 [MNa^+]
273	Cl	^1H -nmr (CDCl_3 , 400MHz) δ : 3.88 (s, 3H), 7.01 (s, 1H), 7.13 (s, 1H) LRMS: m/z (ES^-) 243, 245 [M^-]
274		^1H -nmr (CDCl_3 , 400MHz) δ : 1.78 (m, 1H), 1.92 (m, 1H), 2.35 (m, 2H), 2.52 (m, 2H), 3.88 (s, 3H), 4.73 (m, 1H), 6.30 (s, 1H), 6.69 (s, 1H), 10.83 (s, 1H) LRMS: m/z ES^- 279, 281 [M^-]

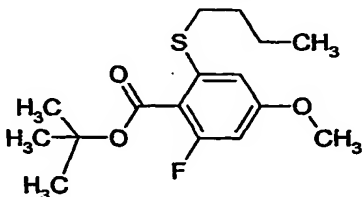
Prep	R	Spectroscopic Data
275		$^1\text{H-nmr}$ (CDCl_3 , 400MHz) δ : 1.63 (m, 1H), 1.94 (m, 2H), 2.69 (m, 1H), 3.90 s, 3H), 4.18 (m, 1H), 6.00 (t, 1H), 6.96 (d, 1H), 7.38 (d, 1H), 10.03 (s, 1H) LRMS: m/z ES^+ 303 [MNa^+]

Preparation 2762,6-Difluoro-4-methoxy-benzoic acid *tert*-butyl ester

- 5 N,N-dimethylformamide di-*tert*-butyl acetal (75 ml, 0.31 mol) in toluene (60 ml) was added dropwise over 1.5 hours to 2,6-difluoro-4-methoxy-benzoic acid (15 g, 80 mmol) (Mol. Cryst. Liq. Cryst. 1989, 172) in toluene (120 ml) at 80°C under a nitrogen atmosphere. The mixture was stirred at 80°C for 30 minutes and then cooled to room temperature. Ethyl acetate (100 ml) was added and the organic solution was washed
- 10 with saturated sodium hydrogen carbonate solution (2x150 ml), brine (150 ml), dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using diethyl ether in pentane as eluant (10:90) to give the title compound as an oil (17.91 g).

$^1\text{H-nmr}$ (CDCl_3 , 400MHz) δ : 1.58 (s, 9H), 3.79 (s, 3H), 6.43 (d, 2H)

- 15 LRMS: m/z ES^+ 267 [MNa^+]

Preparation 2772-Butylsulfanyl-6-fluoro-4-methoxy-benzoic acid *tert*-butyl ester

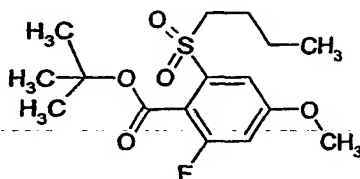
- 20 The ester from preparation 276 (488 mg, 2 mmol) was added to butane-1-thiol (321 μl , 3 mmol) and potassium carbonate (826 mg, 6 mmol) in 1-methyl-pyrrolidin-2-one (4 ml) and the mixture was heated at 120°C for 23 hours. The reaction mixture was partitioned between water (20 ml) and diethyl ether/pentane (50:50, 100 ml) and the

phases were separated. The organic layer was washed with 1M sodium hydroxide solution (2x10 ml) and water (10 ml), then dried over magnesium sulphate and evaporated under reduced pressure to give the title compound as an oil (562 mg).

¹H-nmr (CDCl₃, 400MHz) δ: 0.93 (t, 3H), 1.42 (m, 2H), 1.59 (s, 9H), 1.68 (m, 2H), 2.71 (t, 2H), 3.79 (s, 3H), 6.40 (d, 1H), 6.65 (s, 1H)

Preparation 278

2-(Butane-1-sulfonyl)-6-fluoro-4-methoxy-benzoic acid *tert*-butyl ester

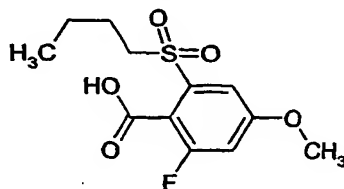


- 10 The thioether from preparation 277 (550 mg, 1.5 mmol) was dissolved in dichloromethane (15 ml) and 3-chloroperoxybenzoic (60-85% pure, 2.4g) was added. The mixture was stirred for 2 hours and then was diluted with dichloromethane (50 ml). The mixture was washed with 30% potassium carbonate solution (2x50 ml) and brine (50 ml), then dried over magnesium sulphate and evaporated under reduced pressure.
- 15 The residue was purified by chromatography on silica gel using diethyl ether in pentane as eluant (gradient from 10:90 to 20:80) to give the title compound as a gum (339 mg). ¹H-nmr (CDCl₃, 400MHz) δ: 0.92 (t, 3H), 1.43 (m, 2H), 1.59 (s, 9H), 1.71 (m, 2H), 3.37 (m, 2H), 3.87 (s, 3H), 6.82 (d, 1H), 7.30 (s, 1H)
- LRMS: *m/z* ES⁺ 369 [MNa⁺]

20

Preparation 279

2-(Butane-1-sulfonyl)-6-fluoro-4-methoxy-benzoic acid



- Trifluoroacetic acid (3 ml) was added to the ester from preparation 278 (320 mg, 0.92 mmol) in dichloromethane (3 ml) and the mixture was stirred for 2 hours at room temperature. The solvent was evaporated under reduced pressure and the last traces of trifluoroacetic acid were removed by dichloromethane azeotrope (3x10 ml) to give the title compound as a gum (288 mg).

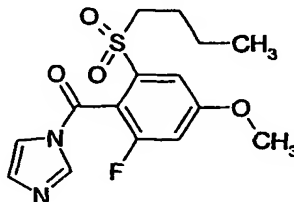
^1H -nmr (CDCl_3 , 400MHz) δ : 0.92 (t, 3H), 1.44 (m, 2H), 1.76 (m, 2H), 3.40 (t, 2H), 3.92 (s, 3H), 6.88 (d, 1H), 7.37 (s, 1H)

LRMS: m/z (ES^-) 289 [$\text{M}-\text{H}$] $^-$

5

Preparation 280

[2-(Butane-1-sulfonyl)-6-fluoro-4-methoxy-phenyl]-imidazol-1-yl-methanone



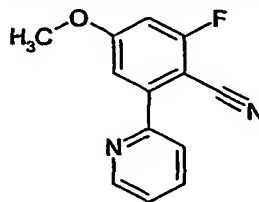
The carboxylic acid from preparation 279 (288 mg, 0.92 mmol) was dissolved in N,N-dimethylformamide (4 ml) and 1,1'-carbonyldiimidazole (164 mg, 1 mmol) was added under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1.5 hours and then was diluted with N,N-dimethylformamide (2 ml).

The resulting solution was used without further elaboration in Example 127 and Example 128.

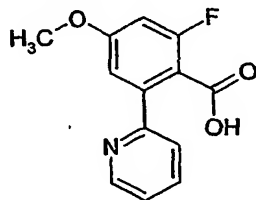
15

Preparation 281

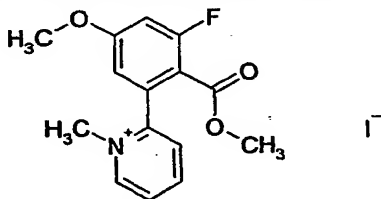
2-Fluoro-4-methoxy-6-pyridin-2-yl-benzonitrile



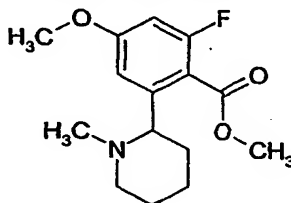
The iodo compound from preparation 241 (1 g, 3.6 mmol) was mixed with 2-tributylstannanyl-pyridine (2.66 g, 7.2 mmol), copper (I) iodide (137 mg, 0.72 mmol), lithium chloride (612 mg, 14.2 mmol) and tetrakis(triphenylphosphine)palladium(0) (400 mg, 0.34 mmol) in 1,4-dioxane (25 ml) and the mixture was heated under reflux for 4 hours. The reaction was cooled to room temperature and concentrated ammonium hydroxide solution (5 ml) was added. The solution was partitioned between brine and dichloromethane and the aqueous phase was extracted with dichloromethane. The combined organic solutions were dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ethyl acetate in pentane as eluant (gradient from 50:50 to 100:0) to give the title compound as a pale yellow solid (0.95 g). LRMS: m/z ES^+ 229 [MH^+]

Preparation 2822-Fluoro-4-methoxy-6-pyridin-2-yl-benzoic acid

- The nitrile from preparation 281 (500 mg) was added to concentrated hydrochloric acid (15 ml) and the mixture was heated under reflux for 6 hours. The reaction mixture was cooled to room temperature and adjusted to pH5 by addition of 5N sodium hydroxide. The solution was extracted with dichloromethane (3x50 ml) and ethyl acetate (3x10 ml) and the combined organic solutions were dried over magnesium sulphate and evaporated under reduced pressure to give the title compound (420 mg).
- LRMS: m/z ES⁺ 248 [MH⁺]

Preparation 2832-(3-Fluoro-5-methoxy-2-methoxycarbonyl-phenyl)-1-methyl-pyridinium iodide

- The pyridylbenzoic acid from preparation 282 (282 mg, 1.1 mmol) and iodomethane (1.42 g, 10 mmol) in acetonitrile (10 ml) were stirred at room temperature for 16 hours. N,N-Diisopropylethylamine (142 mg, 1.1 mmol) was added and the mixture was stirred at room temperature for 4 hours and then was heated under reflux for 2.5 hours. The reaction mixture was cooled to room temperature and was stirred for 16 hours. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (10:90). The material obtained was triturated with diethyl ether to give the title compound as a yellow solid (416 mg).
- ¹H-nmr (DMSO-d₆ 400MHz) δ : 3.60 (s, 3H), 3.90 (s, 3H), 4.00 (s, 3H), 7.12 (s, 1H), 7.27 (d, 1H), 7.99 (d, 1H), 8.15 (m, 1H), 8.60 (m, 1H), 9.12 (d, 1H)
- LRMS: m/z ES⁺ 291 [MNa⁺]

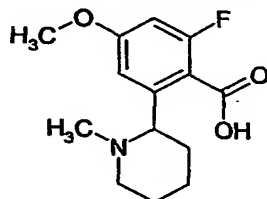
Preparation 2842-Fluoro-4-methoxy-6-(1-methyl-piperidin-2-yl)-benzoic acid methyl ester

5 The pyridinium iodide from preparation 283 (410 mg, 1mmol) was added to platinum oxide (100 mg) in methanol (50 ml) under a nitrogen atmosphere and ammonium formate (3.3 g) was added. The mixture was heated under reflux for 2 hours, cooled to room temperature and stirred for 16 hours. Additional platinum oxide (100 mg) and ammonium formate (3.3 g) were added and the mixture was heated under reflux for 1 hour. The reaction mixture was cooled to room temperature, diluted with dichloromethane (150 ml) and filtered through Arbocel®. The filter cake was washed with dichloromethane and water and the filtrate was diluted with water. The organic layer was separated, dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 0:100 to 4:96) to give the title compound as an orange oil (150 mg).

¹H-nmr (CDCl₃, 400MHz) δ: 1.63 (m, 6H), 2.00 (s, 3H), 2.10 (m, 1H), 2.97 (m, 2H), 3.80 (s, 3H), 3.88 (s, 3H), 6.51 (d, 1H), 6.93 (s, 1H)

LRMS: *m/z* ES⁺ 282 [MH⁺]

20

Preparation 2852-Fluoro-4-methoxy-6-(1-methyl-piperidin-2-yl)-benzoic acid

25 The methyl ester from preparation 284 (215 mg, 0.76 mmol) and 1M sodium hydroxide solution (0.8 ml, 0.8 mmol) were mixed in methanol (10 ml) and the solution was heated under reflux for 2 hours. Additional 2M sodium hydroxide solution (1 ml, 2 mmol) was added and the mixture was heated under reflux for a further 6 hours. The reaction mixture was cooled to room temperature and 2M hydrochloric acid (1.5 ml) was added. The mixture was evaporated under reduced pressure and the residue was

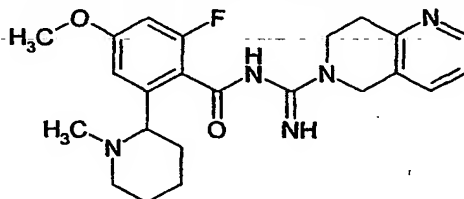
purified by chromatography on silica gel using methanol and ammonium hydroxide in dichloromethane as eluant (10:1:90). The material obtained was triturated with diethyl ether to give the title compound as a white solid (173 mg).

¹H-nmr (DMSO-d₆, 400MHz) δ: 1.98 (m, 9H), 2.47 (m, 1H), 3.27 (m, 2H), 3.81 (s, 3H), 6.50 (s, 1H), 6.64 (d, 1H)

LRMS: *m/z* ES⁺ 268 [MH⁺]

Preparation 286

N-[(7,8-Dihydro-5H-[1,6]naphthyridin-6-yl)-imino-methyl]-2-fluoro-4-methoxy-6-(1-methyl-piperidin-2-yl)-benzamide



The guanidine from preparation 225 (121 mg, 0.3 mmol) was suspended in N,N-dimethylformamide (3 ml) and sodium hydride (60% in mineral oil, 60 mg, 1.5 mmol) was added and the mixture was stirred at room temperature for 20 minutes.

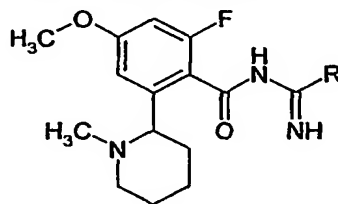
The carboxylic acid from preparation 285 (80 mg, 0.3 mmol) was suspended in dichloromethane (4 ml) containing 1 drop of N,N-dimethylformamide. Oxalyl chloride (76 mg, 0.6 mmol) was added and the mixture was stirred for 10 minutes. The mixture was evaporated under reduced pressure and the residue was redissolved in dichloromethane (3 ml). The solution obtained was added to the guanidinium salt described above and the mixture was stirred at room temperature for 1 hour and then was acidified with 0.2N hydrochloric acid (50 ml). The solution was washed with dichloromethane (2x20 ml) and then basified with 1M sodium hydroxide. The aqueous mixture was extracted with dichloromethane (3x70 ml) and the combined extracts were dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol and ammonium hydroxide in dichloromethane as eluant (7:1:93) to give the title compound as a glass (78 mg).

¹H-nmr (CDCl₃, 400MHz) δ: 1.23 (m, 1H), 1.65 (m, 5H), 1.84 (m, 1H), 2.06 (s, 3H), 2.98 (m, 1H), 3.10 (t, 2H), 3.17 (m, 1H), 3.80 (s, 3H), 3.86 (t, 2H), 4.75 (s, 2H), 6.50 (d, 1H), 6.94 (s, 1H), 7.11 (m, 1H), 7.38 (d, 1H), 7.80 (s, 2H), 8.45 (d, 1H)

LRMS: *m/z* ES⁺ 426 [MH⁺]

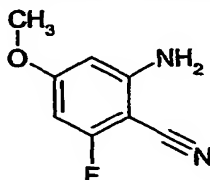
Preparations 287 to 288

The compounds of the following tabulated preparations of the general formula:

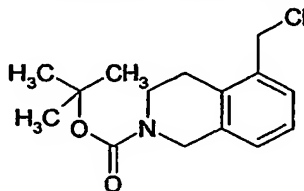


- 5 were prepared by a similar method to that of preparation 286 using the carboxylic acid from preparation 285 and the appropriate guanidine.

Prep	R	Spectroscopic Data
287		$^1\text{H-nmr}$ (CDCl_3 , 400MHz) δ : 1.55 (m, 5H), 2.08 (m, 5H), 2.83 (t, 2H), 3.00 (m, 1H), 3.20 (m, 1H), 3.85 (t, 2H), 4.82 (m, 9H), 4.61 (s, 2H), 6.51 (d, 1H), 6.61 (s, 1H), 6.68 (s, 1H), 6.97 (s, 1H), 7.66 (s, 2H) LRMS: m/z ES ⁻ 483 [M ⁻ H]
288		$^1\text{H-nmr}$ (CDCl_3 , 400MHz) δ : 1.26 (m, 1H), 1.62 (m, 4H), 2.00 (m, 5H), 2.87 (t, 2H), 2.95 (m, 1H), 3.18 (m, 1H), 3.38 (s, 3H), 3.47 (m, 2H), 3.55 (t, 2H), 3.80 (m, 5H), 4.53 (s, 2H), 4.72 (m, 1H), 6.28 (d, 1H), 6.49 (d, 1H), 6.93 (s, 1H), 7.10 (d, 1H), 7.70 (s, 2H) LRMS: m/z ES ⁻ 497 [M ⁻ H]

Preparation 2892-Amino-6-fluoro-4-methoxy-benzonitrile

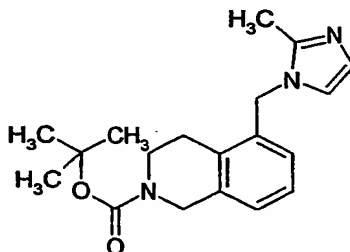
- 10 2,6-Difluoro-4-methoxy-benzonitrile (Mol. Cryst. Liq. Cryst. 1989, 172) (200 mg, 1.18 mmol) was dissolved in ethanolic ammonia (2M solution, 10 ml) and the mixture was heated at 140°C in an autoclave for 16 hours. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ethyl acetate in pentane as
- 15 eluant (20:80) to give the title compound as a white solid (165 mg). LRMS: m/z (ES⁺) 189 [MNa⁺]

Preparation 2905-Chloromethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

- 5 Triethylamine (160 μ l, 1.16 mmol) and then methane sulphonyl chloride (72 μ l, 0.92 mmol) were added to 5-hydroxymethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (202 mg, 0.77 mmol) (WO 02053558 p 59) in tetrahydrofuran (20 ml) and the mixture was stirred for 30 minutes. Tetrabutyl ammonium chloride (322 mg, 1.16 mmol) was added and the mixture was stirred for 2 hours at room temperature.
- 10 The reaction mixture was diluted with ethyl acetate and the organic solution was washed with sodium hydrogen carbonate solution, dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (2:98) to give the title compound (100 mg).
- 15 ^1H -nmr (CDCl_3 , 400MHz) δ : 1.43 (s, 9H), 2.92 (m, 2H), 3.70 (m, 2H), 4.39 (s, 4H), 7.18 (m, 3H)
- LRMS: m/z (ES^+) 304 [MNa^+]

Preparation 291

- 20 5-(2-Methyl-imidazol-1-ylmethyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester



- Sodium hydride (60% in mineral oil, 48 mg, 1.2 mmol) was added to 2-methylimidazole (103 mg, 1.25 mmol) in tetrahydrofuran (10 ml) under a nitrogen atmosphere. The mixture was stirred for 1.5 hours and then the chloromethyl compound from preparation 290 (325 mg, 1.15 mmol) was added in tetrahydrofuran (1 ml). The mixture was heated under reflux for 2 hours and then cooled to room temperature and stirred at
- 25

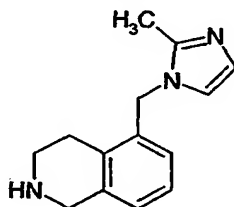
room temperature for 16 hours. The reaction mixture was partitioned between ethyl acetate (75 ml) and water (75 ml). The phases were separated and the aqueous solution was extracted with ethyl acetate (2x35 ml). The combined ethyl acetate layers were dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ammonium hydroxide and methanol in dichloromethane as eluant (gradient from 0:0:100 to 0.5:5:95) to give the title compound as a pale yellow oil (383 mg).

¹H-nmr (CDCl₃, 400MHz) δ: 1.46, (s, 9H), 2.33 (s, 3H), 2.68 (t, 2H), 3.66 (t, 2H), 4.59 (s, 2H), 4.97 (s, 2H), 6.65 (m, 2H), 6.96 (s, 1H), 7.12 (m, 2H)

LRMS: m/z (ES⁺) 328 [MH⁺]

Preparation 292

5-(2-Methyl-imidazol-1-ylmethyl)-1,2,3,4-tetrahydro-isoquinoline



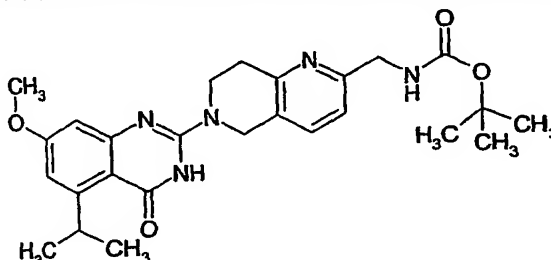
The protected amine from preparation 291 (290 mg, 0.88 mmol) was dissolved in dichloromethane (12 ml) and was cooled to 4°C under a nitrogen atmosphere. Hydrogen chloride was bubbled into the solution for 10 minutes to give a saturated solution. The reaction mixture was stirred at 4°C for 2.5 hours and then evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ammonium hydroxide and methanol in dichloromethane as eluant (0.7: 7: 93). The material obtained was co evaporated with methanol to give the title compound as a pale yellow oil (180 mg).

¹H-nmr (CDCl₃, 400MHz) δ: 2.33 (s, 3H), 2.60 (t, 2H), 3.18 (t, 2H), 4.02 (s, 2H), 4.96 (s, 2H), 6.58 (d, 1H), 6.71 (s, 1H), 6.96 (s, 1H), 6.99 (d, 1H), 7.10 (m, 1H)

LRMS: m/z (ES⁺) 228 [MH⁺]

Preparation 293

[6-(5-Isopropyl-7-methoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-5,6,7,8-tetrahydro-[1,6]naphthyridin-2-ylmethyl]-carbamic acid *tert*-butyl ester



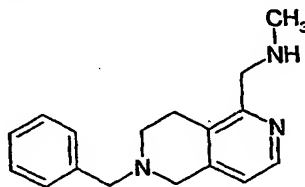
- 5 The chloro compound from preparation 269 (101 mg, 0.4 mmol) was added to the amine from preparation 182 (116 mg, 0.44 mmol) and triethylamine (168 μ l, 1.2 mmol) in *n*-butanol (8 ml) and the mixture was heated under reflux for 2 hours. The reaction mixture was cooled to room temperature and was stirred for 16 hours. The solid formed was isolated by filtration and was washed with diethyl ether (20 ml), water (10 ml) and diethyl ether (40 ml). The residue was dried under vacuum at 90°C for 4 hours to give the title compound (160 mg).

¹H-nmr (DMSO-d₆ 400MHz) δ : 1.15 (d, 6H), 1.38 (s, 9H), 2.92 (t, 2H), 3.80 (s, 3H), 3.92 (t, 2H), 4.15 (d, 2H), 4.53 (m, 1H), 4.78 (s, 2H), 6.80 (d, 1H), 7.10 (m, 2H), 7.18 (m, 1H), 7.58 (d, 1H)

- 15 LRMS: *m/z* (ES⁺) 502 [MNa⁺]

Preparation 294

(6-Benzyl-5,6,7,8-tetrahydro-[2,6]naphthyridin-1-ylmethyl)-methyl-amine



20

Methylamine (40% in water, 1 ml) and acetic acid (60 μ l, 1 mmol) were added to the aldehyde from preparation 35 (115 mg, 0.46 mmol) in tetrahydrofuran (6 ml). The mixture was stirred at room temperature for 5 minutes and then sodium triacetoxyborohydride (636 mg, 3 mmol) was added. The mixture was stirred at room temperature for 1 hour and then was acidified with 2M hydrochloric acid. The mixture was stirred for 10 minutes and then basified with 1M sodium hydroxide. The reaction mixture was extracted with 5% methanol in dichloromethane (4x40 ml) and the

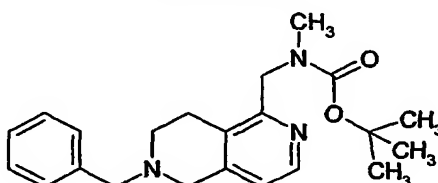
25

combined organic solutions were dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ammonium hydroxide and methanol in dichloromethane as eluant (1:7:93) to give the title compound as a yellow oil (57 mg).

5 LRMS: m/z (ES^+) 268 [MH^+]

Preparation 295

(6-Benzyl-5,6,7,8-tetrahydro-[2,6]naphthyridin-1-ylmethyl)-methyl-carbamic acid tert-butyl ester



10

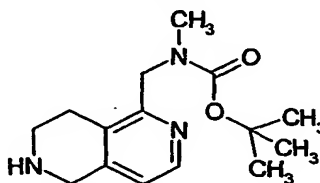
The amine from preparation 294 (57 mg, 0.21 mmol) was dissolved in dichloromethane and di-*tert*-butyl dicarbonate (55 mg, 0.25 mmol) was added. The mixture was stirred at room temperature for 2 hours then the reaction mixture was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 0:100 to 5:95) to give the title compound as an oil (61 mg).

15

LRMS: m/z (ES^+) 390 [MNa^+]

Preparation 296

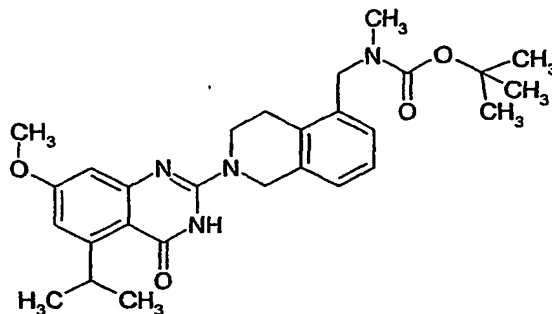
Methyl-(5,6,7,8-tetrahydro-[2,6]naphthyridin-1-ylmethyl)-carbamic acid tert-butyl ester



20

The title compound was obtained as a colourless oil from the benzyl compound from preparation 295 in 72% yield following the procedure described in preparation 109.

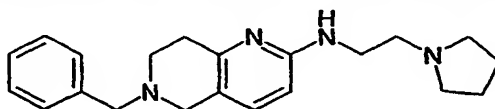
LRMS: m/z (ES^+) 300 [MNa^+]

Preparation 297[2-(5-Isopropyl-7-methoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-1,2,3,4-tetrahydro-isoquinolin-5-ylmethyl]-methyl-carbamic acid tert-butyl ester

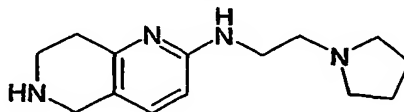
- 5 The chloro compound from preparation 269 (31 mg, 0.12 mmol) was added to the amine from preparation 296 (34 mg, 0.12 mmol) in n-butanol (2 ml) containing N,N-diisopropylethylamine (129 μ l, 1 mmol) and the mixture was heated under reflux for 2.5 hours. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 0:100 to 5:95) to give the title compound as an oil (59 mg).
- 10 LRMS: m/z (ES⁺) 516 [MNa⁺]

Preparation 298

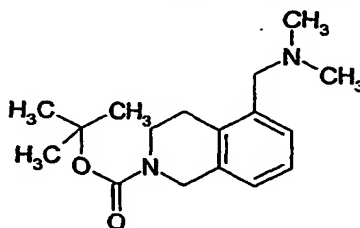
- 15 (6-Benzyl-5,6,7,8-tetrahydro-[1,6]naphthyridin-2-yl)-(2-pyrrolidin-1-yl-ethyl)-amine



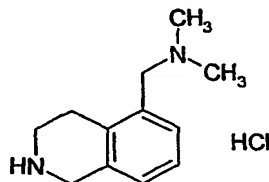
- Copper (II) sulphate (70 mg) was added to a solution of 6-benzyl-2-chloro-5,6,7,8-tetrahydro-[1,6]naphthyridine (0.75 g, 2.9 mmol) (WO9830560 Example 33 b) in 2-pyrrolidin-1-yl-ethylamine (3 ml) and the mixture was heated in an autoclave to 150°C
- 20 for 24 hours. The reaction mixture was cooled to room temperature and was diluted with dichloromethane (50 ml). The solution was washed with 50% ammonium hydroxide solution (50 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (2x50 ml). The combined organic solutions were dried over magnesium sulphate and evaporated under reduced pressure. The residue was
- 25 purified by chromatography on silica gel using ammonium hydroxide and methanol in dichloromethane as eluant (gradient from 0.5:5:95 to 0.7:7:93) to give the title compound as a yellow oil (0.9 g). LRMS: m/z (ES⁺) 337 [MH⁺]

Preparation 299(2-Pyrrolidin-1-yl-ethyl)-(5,6,7,8-tetrahydro-[1,6]naphthyridin-2-yl)-amine

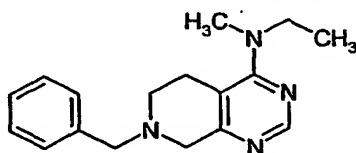
- The title compound was obtained from the benzyl compound from preparation 298 (850 mg, 2.53 mmol) in 56% yield following the procedure described in preparation 109.
- LRMS: m/z (ES⁺) 247 [MH⁺]

Preparation 3005-Dimethylaminomethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

- A solution of the aldehyde from preparation 25 (650 mg, 2.5 mmol), and dimethylamine (2M in tetrahydrofuran, 1.75 ml, 3.5 mmol) in tetrahydrofuran (5 ml) was stirred at room temperature for 3 hours. Sodium triacetoxyborohydride (1.47 g, 7 mmol) was added and the reaction stirred at room temperature for 18 hours. The mixture was partitioned between dichloromethane (50 ml) and sodium bicarbonate solution (30 ml), the layers separated, and the organic phase dried over magnesium sulphate and evaporated under reduced pressure. The residual oil was purified by chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (98:2:0.2) as eluant to afford the title compound, 602mg.
- ¹H-nmr (CDCl₃, 400MHz) δ : 1.50 (s, 9H), 2.20 (s, 6H), 2.90 (t, 2H), 3.35 (s, 2H), 3.62 (t, 2H), 4.55 (s, 2H), 7.00 (m, 1H), 7.10 (d, 2H).

Preparation 301Dimethyl-(1,2,3,4-tetrahydro-isoquinolin-5-ylmethyl)-amine hydrochloride

The title compound was obtained from the protected amine from preparation 300 (575 mg, 2 mmol) in quantitative yield following the procedure described in preparation 212.
LRMS: m/z (ES⁺) 213 [MNa⁺]

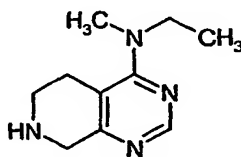
Preparation 302(7-Benzyl-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-ethyl-methylamine

10

A mixture of the chloride from preparation 39 (1.20 g, 4.68 mmol) and N-methylethylamine (2 ml) in dichloromethane (10 ml) was stirred at room temperature for 18 hours, then under reflux for a further 8 hours. Acetonitrile (20 ml) was added, and the reaction stirred under reflux for an additional 24 hours. The cooled mixture was concentrated under reduced pressure and the residue partitioned between dichloromethane and 1% sodium bicarbonate solution. The organic layer was separated, dried over magnesium sulphate, and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel using dichloromethane:methanol (100:0 to 94:6) to afford the title compound as a pale yellow oil, 1.26g.

20

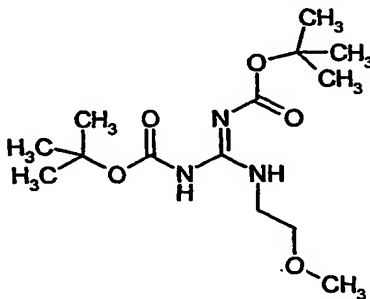
LRMS : m/z (ES⁺) 283 [MH⁺]

Preparation 303Ethyl-methyl-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)amine

- 5 A mixture of the protected amine from preparation 302 (1.17 g, 4.15 mmol), ammonium formate (11.7 g) and 10% palladium on charcoal (1.11 g) in methanol (50 ml) was heated under reflux for 40 minutes. The cooled mixture was filtered through Arbocel®, and the filtrate poured into 1N sodium hydroxide solution. This mixture was continually extracted with dichloromethane for 4 hours, and the organic extract evaporated under reduced pressure. The crude product was purified by chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (90:9:1) to give the title product as a clear oil, 600 mg.

LRMS : m/z (ES⁺) 193 [MH⁺]

15

Preparation 304tert-Butyl [(tert-butoxycarbonyl)amino][(2-methoxyethyl)amino]methylenecarbamate

- Mercury chloride (11.94 g, 44 mmol) was added to a rapidly stirring solution of 2-methoxyethylamine (3.0 g, 40 mmol), 1,3-bis(tert-butoxycarbonyl)-2-methyl-2-thiopseudourea (11.6 g, 40 mmol) and triethylamine (20.24 g, 200 mmol) in dichloromethane (100 ml), and the reaction stirred at room temperature for 17 hours. The mixture was filtered, the filtrate evaporated under reduced pressure and the residue triturated with hot ethyl acetate to remove further mercury salts. The filtrate was evaporated under reduced pressure and the crude product purified by chromatography on silica gel using cyclohexane:ethyl acetate (95:5 to 85:15) to give the title compound as a colourless oil, 8.2 g.

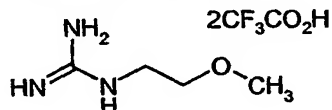
^1H -nmr (CDCl_3 , 400MHz) δ : 1.45 (s, 18H), 3.38 (s, 3H), 3.48 (m, 2H), 3.61 (m, 2H), 8.48 (bs, 1H).

LRMS : m/z (ES^+) 340 [MNa^+]

5

Preparation 305

N-(2-Methoxyethyl)guanidine trifluoroacetate



A solution of the compound from preparation 304 (8.1 g, 25.5 mmol) in trifluoroacetic acid (60 ml) was stirred at room temperature for 4 hours. The reaction was concentrated under reduced pressure and the residue azeotroped with toluene and then dichloromethane. The residue was dried in vacuo at 60°C to afford the title compound as a colourless oil, 8.77 g.

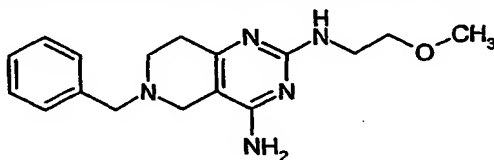
10

^1H -nmr (DMSO-d_6 , 400MHz) δ : 3.23 (m, 5H), 3.40 (m, 2H), 7.05 (bs, 4H), 7.55 (bs, 1H).

15

Preparation 306

6-Benzyl-N²⁺-(2-methoxyethyl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidine-2,4-diamine



Sodium hydride (156 mg, 60% dispersion in mineral oil, 3.9 mmol) was added portionwise to dry ethanol (3.5 ml), and once addition was complete, the guanidine from preparation 305 (621 mg, 1.8 mmol) was added, and the solution heated under reflux for 30 minutes. 4-Amino-1-benzyl-1,2,5,6-tetrahydro-3-pyridinecarbonitrile (J. Med. Chem. 1991; 34 (9); 2899) (213 mg, 1 mmol) was added and the reaction heated under reflux for a further 17 hours. TLC analysis showed starting material remaining, so the cooled reaction was diluted with ethanol (3 ml), additional sodium hydride (10 mg, 60% dispersion in mineral oil, 0.4 mmol) added, and the reaction heated under reflux for a further 24 hours. The cooled mixture was partitioned between water (50 ml) and ethyl acetate (50 ml), the layers separated, the aqueous extracted with ethyl acetate (2x35 ml), and the combined organic solutions dried over magnesium sulphate and evaporated under reduced pressure. The residual oil was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (97:3:0.2

20

25

30

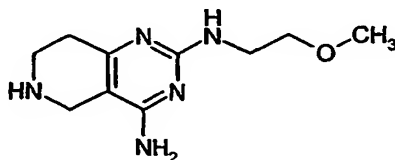
to 90:10:1) and the product azeotrope with ether to afford the title compound as a yellow solid, 58 mg.

¹H-nmr (CDCl₃, 400MHz) δ: 2.68 (t, 2H), 2.78 (t, 2H), 3.22 (s, 2H), 3.37 (s, 3H), 3.52 (m, 4H), 3.70 (s, 2H), 4.32 (bs, 2H), 4.95 (s, 1H), 7.22-7.38 (m, 5H).

5

Preparation 307

N²-(2-methoxyethyl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidine-2,4-diamine



Ammonium formate (10 g, 158.5 mmol) was added to a mixture of the compound from preparation 306 (1.07 g, 3.41 mmol) and 10% palladium on charcoal (1.0 g) in methanol (75 ml), and the reaction heated under reflux for 35 minutes. The cooled mixture was filtered through Arbocel®, washing well with ethanol, and the combined filtrates evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (95:5:0.5 to 85:12:2) and the product azeotrope with methanol and ether to afford the title compound as a white solid, 218 mg.

15

¹H-nmr (DMSO-d₆, 400MHz) δ: 2.37 (m, 2H), 2.82-3.50 (m, 12H), 5.63 (s, 1H), 5.80 (bs, 2H).

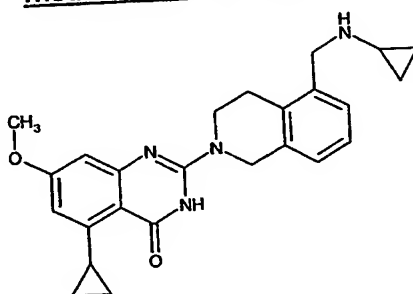
LRMS : m/z (ES⁺) 224 [MH⁺]

20

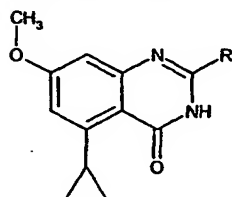
The invention is illustrated by the following examples:

Example 1

5-Cyclopropyl-2-(5-[(cyclopropylamino)methyl]-3,4-dihydro-2(1H)-isoquinolinyl)-7-methoxy-4(3H)-quinazolinone

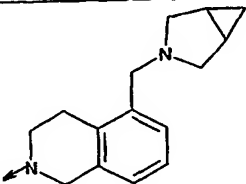
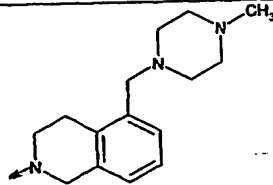
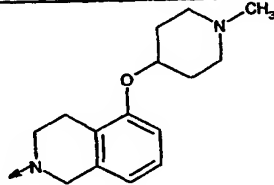


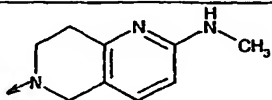
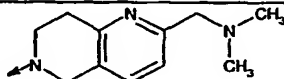
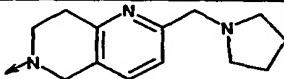
- A mixture of the amine hydrochloride from preparation 95 (113mg, 0.41mmol), the chloride from preparation 18 (86mg, 0.34mmol) and diisopropylethylamine (0.36mL, 1.7mmol) in n-butanol (3mL) was stirred under reflux for 2.5 hours. The cooled reaction mixture was concentrated under reduced pressure and the residue partitioned between dichloromethane (40mL) and water. The layers were separated, the organic phase washed with brine, dried (MgSO₄) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using dichloromethane:methanol (97:3) as eluant to afford the title compound as a solid.
- ¹Hnmr (DMSO-d₆, 400MHz) δ: 0.13 (m, 2H), 0.35 (m, 2H), 0.63 (m, 2H), 0.90 (m, 2H), 2.07 (m, 2H), 2.90 (m, 2H), 3.49 (m, 1H), 3.68 (s, 2H), 3.75 (m, 4H), 3.83 (m, 2H), 4.75 (s, 2H), 6.13 (m, 1H), 6.48 (m, 1H), 7.05 (m, 1H), 7.15 (m, 1H), 10.82 (bs, 1H).
- LRMS : m/z (ES⁺) 417 [MH⁺]
- Microanalysis found: C, 69.56; H, 6.54; N, 13.04. C₂₅H₂₈N₄O₂·0.8H₂O requires C, 69.69; H, 6.92; N, 13.00%.

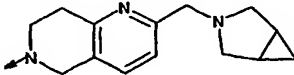
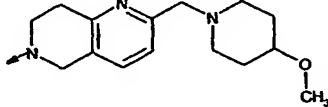
Examples 2 to 25**General Method**

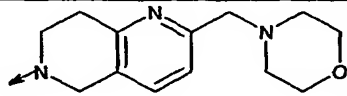
- 5 To a solution of the chloro-quinazolinone from preparation 18 (1eq) in *n*-butanol (15mL per mmol) under nitrogen was added diisopropylethylamine (A) or triethylamine (B) (1.7-8.0 eq) and the appropriate secondary amine (1-2eq). The resultant mixture was then heated at reflux for 1-6 hours, cooled and the product was isolated by filtration, washing with *n*-butanol and diethyl ether.

Ex. no.	R	Base	Yield %/ Form	Spectroscopic and Analytical Data
2 (a)		A	29 white solid	¹ Hnmr (DMSO-d ₆ , 400MHz) δ: 0.30 (m, 2H), 0.40 (m, 2H), 0.63 (m, 2H), 0.94 (m, 2H), 1.73 (m, 1H), 2.10 (s, 3H), 2.90 (m, 2H), 3.46 (m, 1H), 3.60 (s, 2H), 3.77 (s, 3H), 3.80 (m, 2H), 4.77 (s, 2H), 6.13 (s, 1H), 6.53 (s, 1H), 7.10 (m, 3H), 10.84 (bs, 1H). LRMS: m/z (ES ⁺) 453 [MNa ⁺] Microanalysis found: C, 72.07; H, 7.00; N, 12.94. C ₂₆ H ₃₀ N ₄ O ₂ ·0.2H ₂ O requires C, 71.93; H, 7.06; N, 12.90%.

Ex. no.	R	Base	Yield%/Form	Spectroscopic and Analytical Data
3		B	76 white powder	¹ Hnmr (DMSOd ₆ , 400MHz) δ: 0.27 (m, 1H), 0.57 (m, 1H), 0.63 (m, 2H), 0.94 (m, 2H), 1.35 (m, 2H), 2.31 (m, 2H), 2.77 (d, 2H), 2.86 (m, 2H), 3.50 (m, 3H), 3.74 (s, 3H), 3.80 (m, 2H), 4.76 (s, 2H), 6.13 (s, 1H), 6.32 (s, 1H), 7.10 (m, 3H), 10.97 (bs, 1H). LRMS : m/z (ES ⁺) 465 [MNa ⁺] Microanalysis found: C, 72.83; H, 6.83; N, 12.52. C ₂₇ H ₃₀ N ₄ O ₂ ·0.1C ₄ H ₉ OH requires C, 73.14; H, 6.94; N, 12.45%.
4		A	88 white solid	¹ Hnmr (CDCl ₃ , 400MHz) δ: 0.70 (m, 2H), 0.97 (m, 2H), 2.26 (s, 3H), 2.44 (m, 8H), 3.06 (t, 2H), 3.41 (m, 1H), 3.46 (s, 2H), 3.85 (s, 3H), 3.91 (t, 2H), 4.87 (s, 2H), 6.29 (s, 1H), 6.67 (d, 1H), 7.11 (dd, 1H), 7.15 (d, 2H), 10.01 (bs, 1H). LRMS : m/z (ES ⁺) 482 [MNa ⁺]
5 (a)		A	43 white solid	¹ Hnmr (DMSOd ₆ , 400MHz) δ: 0.64 (m, 2H), 0.90 (m, 2H), 1.67 (m, 2H), 1.87 (m, 2H), 2.17 (s, 3H), 2.25 (m, 2H), 2.47 (s, 3H), 2.65 (m, 2H), 2.74 (t, 2H), 3.49 (m, 1H), 3.83 (t, 2H), 4.37 (m, 1H), 4.73 (s, 2H), 6.13 (s, 1H), 6.52 (s, 1H), 6.75 (d, 1H), 6.83 (d, 1H), 7.11 (dd, 1H), 11.00 (bs, 1H). LRMS : m/z (ES ⁺) 461 [MH ⁺]. Microanalysis found: C, 69.55; H, 7.09; N, 11.78. C ₂₇ H ₃₂ N ₄ O ₃ ·0.3H ₂ O requires C, 69.59; H, 7.05; N, 12.02%.

Ex. no.	R	Base	Yield%/Form	Spectroscopic and Analytical Data
6		B	86 white powder	¹ Hnmr (DMSOd ₆ , 400MHz) δ: 0.62 (m, 2H), 0.91 (m, 2H), 2.75 (m, 5H), 3.50 (m, 1H), 3.77 (s, 3H), 3.86 (t, 2H), 4.58 (s, 2H), 6.13 (s, 1H), 6.25 (m, 1H), 6.31 (d, 1H), 6.53 (s, 1H), 7.19 (d, 1H), 10.99 (bs, 1H). LRMS: m/z (ES ⁺) 400 [MNa ⁺]. Microanalysis found: C, 65.18; H, 6.03; N, 18.03. C ₂₁ H ₂₃ N ₅ O ₂ ·0.5H ₂ O requires C, 65.27; H, 6.26; N, 18.12%.
7 (a)		A	35 white solid	¹ H-nmr (DMSO-d ₆ , 400 MHz) δ: 0.64 (m, 2H), 0.93 (m, 2H), 2.16 (s, 6H), 2.93 (t, 2H), 3.47 (m, 3H), 3.76 (s, 3H), 3.93 (t, 2H), 4.78 (s, 2H), 6.15 (s, 1H), 6.53 (s, 1H), 7.24 (d, 1H), 7.57 (d, 1H), 11.08 (bs, 1H). LRMS: m/z (ES ⁺) 404 [M-H]. Microanalysis found: C, 67.08; H, 6.72; N, 16.98. C ₂₃ H ₂₇ N ₅ O ₂ ·0.3H ₂ O requires C, 67.23; H, 6.77; N, 17.04%.
8 (a)		A	51 white solid	¹ H-nmr (DMSO-d ₆ , 400 MHz) δ : 0.64 (m, 2H), 0.93 (m, 2H), 1.70 (m, 4H), 2.53 (m, 4H), 2.94 (t, 2H), 3.50 (m, 1H), 3.69 (s, 2H), 3.76 (s, 3H), 3.93 (t, 2H), 4.78 (s, 2H), 6.15 (s, 1H), 6.52 (s, 1H), 7.25 (d, 1H), 7.56 (d, 1H), 11.08 (bs, 1H). LRMS: m/z (ES ⁺) 454 [MNa ⁺]. Microanalysis found: C, 66.72; H, 6.63; N, 15.41. C ₂₅ H ₂₉ N ₅ O ₂ ·0.9H ₂ O requires C, 67.06; H, 6.93; N, 15.64%.

Ex. no.	R	Base	Yield %/ Form	Spectroscopic and Analytical Data
9 (a)		B	31	¹ H-nmr (DMSO-d ₆ , 400 MHz) δ : 0.32 (m, 1H), 0.63 (m, 3H), 0.93 (m, 2H), 1.35 (m, 2H), 2.37 (m, 2H), 2.90 (m, 4H), 3.49 (m, 1H), 3.63 (s, 2H), 3.78 (s, 3H), 3.92 (t, 2H), 4.78 (s, 2H), 6.15 (s, 1H), 6.53 (s, 1H), 7.18 (d, 1H), 7.57 (d, 1H), 11.05 (bs, 1H). LRMS : m/z (ES ⁺) 466 [MNa ⁺]. Microanalysis found: C, 69.91; H, 6.57; N, 15.67. C ₂₆ H ₂₉ N ₅ O ₂ ·0.2H ₂ O requires C, 69.84; H, 6.63; N, 15.66%.
10 (b)		A	83 white solid	¹ H-nmr (DMSO-d ₆ , 400 MHz) δ : 0.62 (m, 2H), 0.94 (m, 2H), 1.40 (m, 2H), 1.80 (m, 2H), 2.16 (m, 2H), 2.62 (m, 2H), 2.96 (m, 2H), 3.16 (m, 1H), 3.20 (s, 3H), 3.50 (s, 2H), 3.78 (s, 3H), 3.96 (m, 2H), 4.22 (m, 1H), 4.78 (s, 2H), 6.18 (m, 1H), 6.56 (bs, 1H), 7.24 (d, 1H), 7.58 (d, 1H), 11.00 (bs, 1H). LRMS : m/z (ES ⁺) 477 [MH ⁺]. Microanalysis found: C, 67.22; H, 6.96; N, 14.40. C ₂₇ H ₃₃ N ₅ O ₃ ·0.5C ₂ H ₅ OH requires C, 67.45; H, 7.28; N, 14.05%.

Ex. no.	R	Base	Yield %/ Form	Spectroscopic and Analytical Data
11 (a)		A	44 white solid	¹ H-nmr (DMSO-d ₆ , 400 MHz) δ : 0.65 (m, 2H), 0.91 (m, 2H), 2.38 (m, 4H), 2.93 (t, 2H), 3.51 (m, 3H), 3.55 (m, 4H), 3.76 (s, 3H), 3.92 (t, 2H), 4.77 (s, 2H), 6.14 (s, 1H), 6.52 (s, 1H), 7.27 (d, 1H), 7.56 (d, 1H), 11.58 (bs, 1H). LRMS : m/z (ES ⁺) 470 [MNa ⁺]. Microanalysis found: C, 66.29; H, 6.50; N, 15.48. C ₂₅ H ₂₉ N ₅ O ₃ ·0.3H ₂ O requires C, 66.29; H, 6.59; N, 15.46%.

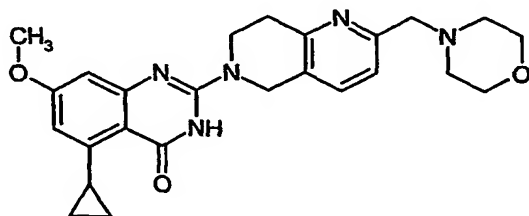
(a) products were additionally purified by column chromatography on silica gel using dichloromethane:methanol or dichloromethane:methanol:0.88 ammonia as eluants.

(b)-ethanol was used as a co-solvent in the reaction

5

Example 11

5-Cyclopropyl-7-methoxy-2-(2-morpholin-4-ylmethyl-7,8-dihydro[1,6]-naphthyridin-6(5H)-yl)-4(3H)-quinazolinone

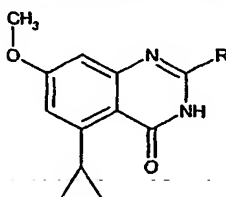


- 10 A mixture of the chloride from preparation 18 (351mg, 1.4mmol) in n-butanol (21mL), the amine from preparation 106 (335mg, 1.43mmol) and N,N-diisopropylethylamine (633mg, 4.9mmol) was heated under reflux for 6 hours, then a further 7 hours at room temperature. The resulting precipitate was filtered off, washed with n-butanol, and dried *in vacuo*. The solid was purified by column chromatography on silica gel using an
- 15 elution gradient of dichloromethane:methanol (97:3 to 93:7), and the product triturated with ether to afford the title compound as a white solid, 470mg.

^1H -nmr (DMSO- d_6 , 400 MHz) δ : 0.65 (m, 2H), 0.91 (m, 2H), 2.38 (m, 4H), 2.93 (t, 2H), 3.51 (m, 3H), 3.55 (m, 4H), 3.76 (s, 3H), 3.92 (t, 2H), 4.77 (s, 2H), 6.14 (s, 1H), 6.52 (s, 1H), 7.27 (d, 1H), 7.56 (d, 1H), 11.58 (bs, 1H). LRMS : m/z (ES^+) 470 [MNa^+].

Microanalysis found: C, 66.29; H, 6.50; N, 15.48. $\text{C}_{25}\text{H}_{29}\text{N}_5\text{O}_3 \cdot 0.3\text{H}_2\text{O}$ requires C, 66.29; H, 6.59; N, 15.46%.

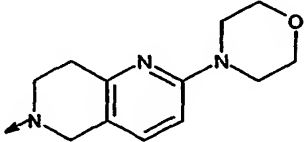
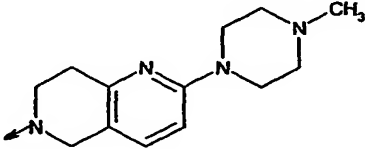
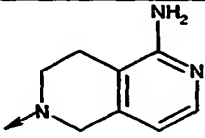
Examples 12 to 25

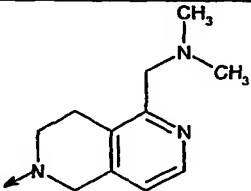
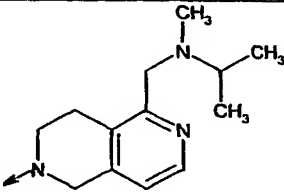
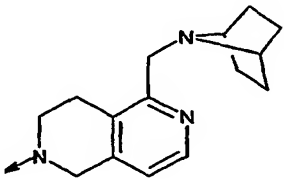


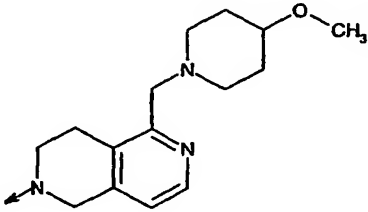
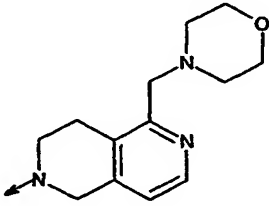
General Method

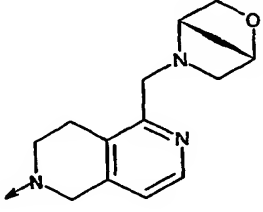
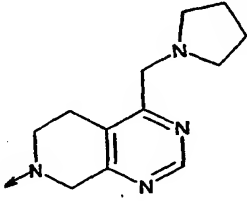
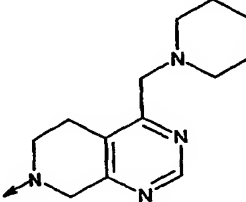
- 10 To a solution of the chloro-quinazolinone from preparation 18 (1eq) in *n*-butanol (15mL per mmol) under nitrogen was added diisopropylethylamine (A) or triethylamine (B) (1.7-8.0 eq) and the appropriate secondary amine (1-2eq). The resultant mixture was then heated at reflux for 1-6 hours, cooled and the product was isolated by filtration, washing with *n*-butanol and diethyl ether.

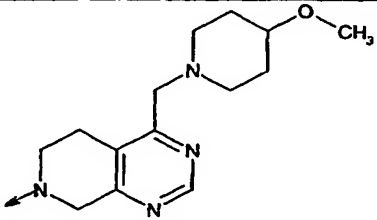
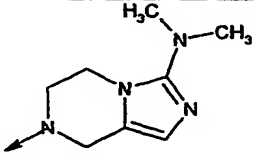
Ex. no.	R	Base	Yield %/ Form	Spectroscopic and Analytical Data
12		A	66 solid	^1H -nmr (DMSO- d_6 , 400 MHz) δ : 0.66 (m, 2H), 0.93 (m, 2H), 1.59 (d, 1H), 1.80 (d, 1H), 2.45 (d, 1H), 2.76 (d, 1H), 2.94 (t, 2H), 3.47 (s, 1H), 3.52 (d, 2H), 3.77 (m, 5H), 3.91 (d, 1H), 3.95 (t, 2H), 4.33 (s, 1H), 4.78 (s, 2H), 6.14 (d, 1H), 6.53 (d, 1H), 7.29 (d, 1H), 7.56 (d, 1H), 11.09 (bs, 1H). LRMS : m/z (ES^+) 460 [MH^+]. Microanalysis found: C, 67.96; H, 6.38; N, 15.12. $\text{C}_{26}\text{H}_{29}\text{N}_5\text{O}_3$ requires C, 67.67; H, 6.38; N, 15.12%.

Ex. no.	R	Base	Yield% /Form	Spectroscopic and Analytical Data
13		B	solid	$^1\text{H-nmr}$ (CDCl_3 , 400 MHz) δ : 0.70 (m, 2H), 1.00 (m, 2H), 2.96 (t, 2H), 3.38 (m, 1H), 3.48 (m, 4H), 3.79 (m, 4H), 3.83 (s, 3H), 3.94 (t, 2H), 4.69 (s, 2H), 6.29 (s, 1H), 6.51 (d, 1H), 6.64 (s, 1H), 7.30 (d, 1H), 9.22 (bs, 1H). LRMS : m/z (ES^+) 456 [MNa^+]
14 (a)		A	62 solid	$^1\text{H-nmr}$ (CDCl_3 , 400 MHz) δ : 0.71 (m, 2H), 0.99 (m, 2H), 2.34 (s, 3H), 2.51 (m, 4H), 2.97 (t, 2H), 3.38 (m, 1H), 3.43 (m, 4H), 3.82 (s, 3H), 3.98 (t, 2H), 4.73 (s, 2H), 6.27 (s, 1H), 6.52 (d, 1H), 6.64 (s, 1H), 7.24 (m, 1H), 9.60 (bs, 1H). LRMS : m/z (ES^+) 469 [MNa^+]
15		A	86 off-white solid	$^1\text{H-nmr}$ (CDCl_3 , 400 MHz) δ : 0.72 (m, 2H), 1.00 (m, 2H), 2.63 (t, 2H), 3.37 (m, 1H), 3.85 (s, 3H), 3.97 (t, 2H), 4.39 (bs, 2H), 4.73 (s, 2H), 6.31 (d, 1H), 6.52 (m, 3H), 6.66 (d, 1H), 7.92 (d, 1H). LRMS : m/z (ES^+) 364 [MH^+]

Ex. no.	R	Base	Yield % /Form	Spectroscopic and Analytical Data
16		A	66 solid	¹ H-nmr (CDCl ₃ , 400 MHz) δ: 0.74 (m, 2H), 0.98 (m, 2H), 2.24 (s, 6H), 3.09 (m, 2H), 3.42 (m, 1H), 3.54 (s, 2H), 3.86 (s, 3H), 4.01 (t, 2H), 4.90 (s, 2H), 6.31 (d, 1H), 6.68 (d, 1H), 7.01 (d, 1H), 8.36 (d, 1H), 10.96 (bs, 1H). LRMS : m/z (ES ⁺) 406 [MH ⁺]. Microanalysis found: C, 67.92; H, 6.73; N, 17.23. C ₂₃ H ₂₇ N ₅ O ₂ requires C, 68.13; H, 6.71; N, 17.27%.
17		B	50 white solid	¹ H-nmr (CDCl ₃ , 400 MHz) δ: 0.63 (m, 2H), 0.91 (m, 2H), 0.98 (d, 6H), 1.97 (s, 3H), 2.80 (m, 1H), 3.00 (m, 2H), 3.51 (m, 1H), 3.61 (s, 2H), 3.77 (s, 3H), 3.85 (t, 2H), 4.78 (s, 2H), 6.15 (s, 1H), 6.54 (s, 1H), 7.13 (d, 1H), 8.22 (d, 1H), 11.12 (bs, 1H). LRMS : m/z (ES ⁺) 432 [M-H ⁺]. Microanalysis found: C, 68.41; H, 7.23; N, 15.76. C ₂₅ H ₃₁ N ₅ O ₂ ·0.25H ₂ O requires C, 68.55; H, 7.25; N, 15.99%.
18		B	61 white solid	¹ H-nmr (CDCl ₃ , 400 MHz) δ: 0.74 (m, 2H), 0.98 (m, 2H), 1.26 (d, 4H), 1.77 (m, 4H), 3.19 (m, 4H), 3.41 (m, 1H), 3.65 (s, 2H), 3.86 (s, 3H), 3.97 (t, 2H), 4.89 (s, 2H), 6.31 (d, 1H), 6.67 (d, 1H), 7.01 (d, 1H), 8.33 (d, 1H), 10.44 (bs, 1H). LRMS : m/z (ES ⁺) 456 [M-H ⁺] Microanalysis found: C, 70.41; H, 6.80; N, 15.13. C ₂₇ H ₃₁ N ₅ O ₂ ·0.25H ₂ O requires C, 70.18; H, 6.87; N, 15.16%.

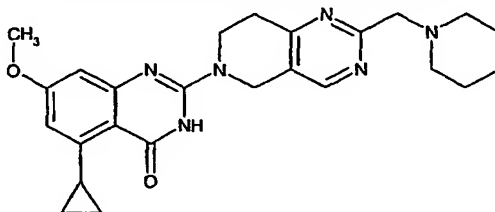
Ex. no.	R	Base	Yield % /Form	Spectroscopic and Analytical Data
19		A	38 white solid	¹ H-nmr (CDCl ₃ , 400MHz) δ: 0.73 (m, 2H), 0.99 (m, 2H), 1.25 (s, 1H), 1.85 (m, 2H), 2.16 (m, 3H), 2.70 (m, 2H), 3.12 (t, 2H), 3.20 (m, 1H), 3.31 (s, 3H), 3.40 (m, 1H), 3.62 (s, 2H), 3.85 (s, 3H), 3.93 (t, 2H), 4.87 (s, 2H), 6.32 (d, 1H), 6.88 (d, 1H), 7.02 (d, 1H), 8.36 (d, 1H). LRMS : m/z (ES ⁺) 476 [MH ⁺] Microanalysis found: C, 66.97; H, 7.00; N, 14.19. C ₂₇ H ₃₃ N ₅ O ₃ ·0.50H ₂ O requires C, 66.92; H, 7.07; N, 14.45%.
20 (a)		B	91 white solid	¹ H-nmr (CDCl ₃ , 400MHz) δ: 0.76 (m, 2H), 0.99 (m, 2H), 2.47 (m, 4H), 3.11 (t, 2H), 3.43 (m, 1H), 3.64 (s, 2H), 3.67 (m, 4H), 3.87 (s, 3H), 4.01 (t, 2H), 4.92 (s, 2H), 6.32 (s, 1H), 6.68 (s, 1H), 7.04 (d, 1H), 8.37 (d, 1H), 10.78 (bs, 1H). LRMS : m/z (ES ⁺) 448 [MH ⁺] Microanalysis found: C, 66.60; H, 6.51; N, 15.63. C ₂₅ H ₂₉ N ₅ O ₃ ·0.20H ₂ O requires C, 66.56; H, 6.59; N, 15.52%.

Ex. no.	R	Base	Yield%/Form	Spectroscopic and Analytical Data
21 (a)		A	25 yellow oil	¹ H-nmr (CDCl ₃ , 400MHz) δ: 0.78 (m, 2H), 1.00 (m, 2H), 1.52-1.80 (m, 4H), 1.98 (m, 1H), 2.78 (m, 1H), 2.98 (m, 1H), 3.18 (m, 2H), 3.42 (m, 1H), 3.63 (m, 1H), 3.90 (s, 3H), 4.00 (m, 2H), 4.17 (m, 1H), 4.42 (m, 1H), 4.90 (s, 2H), 6.35 (d, 1H), 6.67 (d, 1H), 7.02 (d, 1H), 8.37 (d, 1H). LRMS : m/z (ES ⁺) 458 [M-H ⁻]. Microanalysis found: C, 67.48; H, 6.40; N, 15.10. C ₂₆ H ₂₉ N ₅ O ₃ ; requires C, 67.96; H, 6.36; N, 15.24%.
22 (a)		A	54 off-white solid	¹ H-nmr (CDCl ₃ , 400MHz) δ: 0.73 (m, 2H), 1.00 (m, 2H), 1.78 (m, 4H), 2.57 (m, 4H), 3.04 (t, 2H), 3.45 (m, 1H), 3.72 (s, 2H), 3.85 (s, 3H), 4.08 (t, 2H), 4.98 (s, 2H), 6.34 (d, 1H), 6.68 (d, 1H), 8.95 (s, 1H), 11.32 (bs, 1H). LRMS : m/z (ES ⁺) 433 [MH ⁺]. Microanalysis found: C, 66.23; H, 6.50; N, 19.21. C ₂₄ H ₂₈ N ₆ O ₂ requires C, 66.65; H, 6.53; N, 19.43%.
23		A	38 white solid	¹ H-nmr (CDCl ₃ , 400MHz) δ: 0.73 (m, 2H), 0.99 (m, 2H), 1.42 (m, 2H), 1.54 (m, 4H), 2.40 (m, 4H), 3.09 (t, 2H), 3.43 (m, 1H), 3.54 (s, 2H), 3.85 (s, 3H), 4.05 (t, 2H), 4.96 (s, 2H), 6.34 (d, 1H), 6.67 (d, 1H), 8.94 (s, 1H), 10.85 (bs, 1H). LRMS : m/z (ES ⁺) 447 [MH ⁺]. Microanalysis found: C, 66.96; H, 6.82; N, 18.63. C ₂₅ H ₃₀ N ₆ O ₂ requires C, 67.24; H, 6.77; N, 18.82%.

Ex. no.	R	Base	Yield % /Form	Spectroscopic and Analytical Data
24		A	73 solid	¹ H-nmr (CDCl ₃ , 400MHz) δ: 0.73 (m, 2H), 1.01 (m, 2H), 1.55 (m, 2H), 1.84 (m, 2H), 2.23 (m, 2H), 2.71 (m, 2H), 3.07 (t, 2H), 3.22 (m, 1H), 3.31 (s, 3H), 3.42 (m, 1H), 3.57 (s, 2H), 3.85 (s, 3H), 4.06 (t, 2H), 4.97 (s, 2H), 6.34 (d, 1H), 6.67 (d, 1H), 8.94 (s, 1H), 10.96 (bs, 1H). LRMS : m/z (ES ⁺) 477 [MH ⁺]. Microanalysis found: C, 63.66; H, 6.62; N, 17.13. C ₂₆ H ₃₂ N ₆ O ₃ ·0.75H ₂ O requires C, 63.72; H, 6.89; N, 17.15%.
25		A	59 white solid	¹ H-nmr (CDCl ₃ , 400MHz) δ: 0.74 (m, 2H), 1.00 (m, 2H), 2.79 (s, 6H), 3.36 (m, 1H), 3.85 (s, 3H), 3.95 (t, 2H), 4.09 (t, 2H), 4.89 (s, 2H), 6.34 (d, 1H), 6.56 (s, 1H), 6.65 (d, 1H), 10.81 (bs, 1H). LRMS : m/z (ES ⁺) 381 [MH ⁺]. Microanalysis found: C, 61.81; H, 6.25; N, 21.47. C ₂₀ H ₂₄ N ₆ O ₂ ·0.5H ₂ O requires C, 61.68; H, 6.47; N, 21.58%.

(a) products were additionally purified by column chromatography on silica gel using dichloromethane:methanol or dichloromethane:methanol:0.88 ammonia as eluants.

(b)-ethanol was used as a co-solvent in the reaction

Example 265-Cyclopropyl-7-methoxy-2-(2-(1-piperidinylmethyl)-7,8-dihydropyridof[4,3-d]pyrimidin-6(5H)-yl)-4(3H)-quinazolinone

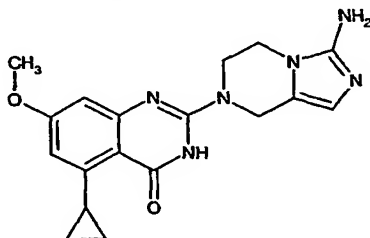
5 A mixture of the chloride from preparation 18 (302mg, 1.2mmol), the amine from preparation 124 (1.23mmol) and diisopropylethylamine (646mg, 5mmol) in n-butanol (10mL) was heated under reflux for 1.5 hours. The cooled mixture was diluted with water and extracted with dichloromethane (3x50mL). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure. The residue was purified
 10 by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 90:10) to afford the title compound as an off-white solid, 307mg.

¹H-nmr (CDCl₃, 400MHz) δ: 0.72 (m, 2H), 0.96 (m, 2H), 1.48 (m, 2H), 1.71 (m, 4H), 2.70 (m, 4H), 3.07 (t, 2H), 3.53 (m, 1H), 3.84 (s, 3H), 3.88 (bs, 2H), 4.06 (t, 2H), 4.89
 15 (s, 2H), 6.31 (s, 1H), 6.66 (s, 1H), 8.51 (s, 1H), 11.12 (bs, 1H).

LRMS : m/z (ES⁺) 447 [MH⁺]

Microanalysis found: C, 65.74; H, 6.83; N, 18.28. C₂₅H₃₀N₆O₂·0.5H₂O requires C, 65.91; H, 6.86; N, 18.45%.

20

Example 272-(3-Amino-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)-5-cyclopropyl-7-methoxy-4(3H)-quinazolinone

The title compound was obtained as a yellow solid in 23% yield, from the chloride from preparation 18 and the amine from preparation 136, following a similar procedure to
 25 that described in example 26, except dichloromethane:methanol:0.88 ammonia (90:10:1) was used as the column eluant.

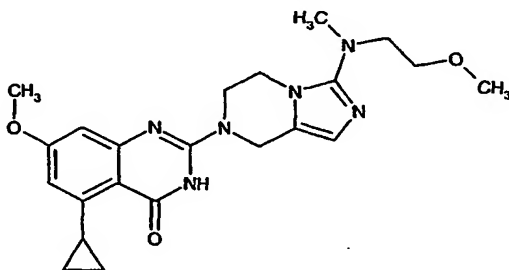
¹H-nmr (DMSO-d₆, 400MHz) δ: 0.64 (m, 2H), 0.2 (m, 2H), 3.48 (m, 1H), 3.75 (m, 5H), 3.93 (t, 2H), 4.68 (s, 2H), 5.48 (s, 2H), 6.16 (s, 1H), 6.28 (s, 1H), 6.53 (s, 1H), 11.10 (bs, 1H).

LRMS : m/z (ES⁺) 353 [MH⁺]

5

Example 28

5-Cyclopropyl-7-methoxy-2-(3-[(2-methoxyethyl)(methyl)amino]-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)-4(3H)-quinazolinone



10 The title compound was obtained as a white solid in 45% yield, from the chloride from preparation 18 and the amine from preparation 133, following a similar procedure to that described in example 26.

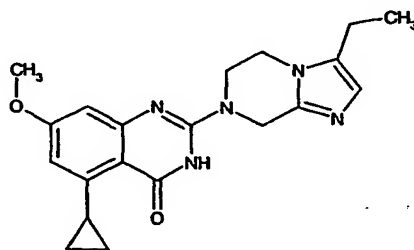
¹H-nmr (CDCl₃, 400MHz) δ: 0.73 (m, 2H), 0.96 (m, 2H), 2.82 (s, 3H), 3.21 (t, 2H), 3.49 (m, 1H), 3.50 (s, 3H), 3.51 (t, 2H), 3.84 (s, 3H), 3.96 (t, 2H), 4.09 (t, 2H), 4.91 (s, 2H),
15 6.33 (d, 1H), 6.55 (s, 1H), 6.65 (d, 1H), 11.38 (bs, 1H).

LRMS : m/z (ES⁺) 425 [MH⁺]

Example 29

5-Cyclopropyl-2-(3-ethyl-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-7-methoxy-4(3H)-quinazolinone

20



The title compound was obtained as a white solid in 43% yield, from the chloride from preparation 18 and the amine from preparation 131, following a similar procedure to that described in example 26, except dichloromethane:methanol:0.88 ammonia
25 (95:50:5) was used as the column eluant.

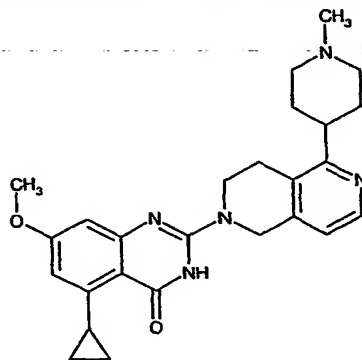
¹H-nmr (DMSO-d₆, 400MHz) δ: 0.62 (m, 2H), 0.96 (m, 2H), 1.16 (t, 3H), 2.52 (m, 2H), 3.50 (m, 1H), 3.78 (s, 3H), 3.92 (m, 2H), 4.04 (m, 2H), 4.78 (s, 2H), 6.18 (s, 1H), 6.56 (s, 1H), 6.60 (s, 1H), 10.80, 11.25 (2xbs, 1H).

LRMS : m/z (ES⁺) 366 [MH⁺]

- 5 Microanalysis found: C, 64.26; H, 6.31; N, 18.10. C₂₀H₂₃N₅O₂·0.15CH₂Cl₂ requires C, 64.00; H, 6.21; N, 18.52%.

Example 30

5-Cyclopropyl-7-methoxy-2-(5-(1-methyl-4-piperidiny)-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone



- 15 A mixture of the chloride from preparation 18 (0.40mmol), the amine hydrochloride from preparation 120 (145.6mg, 0.48mmol) and triethylamine (223μl, 1.60mmol) in n-butanol (6mL) was heated under reflux for 3 hours. The cooled mixture was concentrated under reduced pressure and the residue partitioned between water (4mL) with saturated sodium bicarbonate solution (2mL), and dichloromethane (30mL), and the layers separated. The aqueous phase was extracted with further dichloromethane (2x20mL), and the combined organic solutions dried (MgSO₄) and evaporated under reduced pressure. The residual solid was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (95:5:0.2 to 90:10:0.6) to afford the title compound as a white solid, 110mg.

- 20 ¹H-nmr (DMSO-d₆, 400MHz) δ: 0.64 (m, 2H), 0.93 (m, 2H), 1.60 (m, 2H), 1.83 (m, 2H), 2.04 (m, 2H), 2.21 (s, 3H), 2.80 (m, 1H), 2.87 (m, 4H), 3.40 (m, 1H), 3.76 (s, 3H), 3.89 (t, 2H), 4.77 (s, 2H), 6.15 (s, 1H), 6.51 (d, 1H), 7.04 (d, 1H), 8.30 (d, 1H), 11.07 (bs, 1H).

25 LRMS : m/z (ES⁺) 446 [MH⁺]

Microanalysis found: C, 68.43; H, 7.11; N, 15.35. C₂₆H₃₁N₅O₂·0.6H₂O requires C, 70.09; H, 7.11; N, 15.35%.

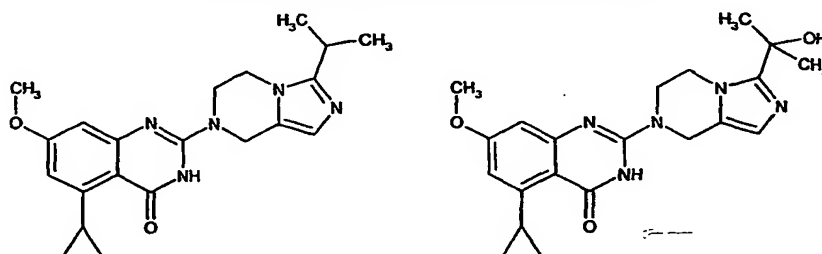
Example 31

5-Cyclopropyl-2-(3-isopropyl-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)-7-methoxy-
4(3H)-quinazolinone

and

Example 32

5-Cyclopropyl-2-(3-(1-hydroxy-1-methylethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-
yl)-7-methoxy-4(3H)-quinazolinone

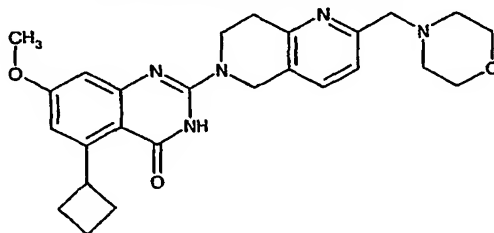


A mixture of the chloride from preparation 18 (80mg, 0.32mmol), the amines from preparations 120 and 121 (99mg), and triethylamine (178 μ l, 1.28mmol) in *n*-butanol (6mL) was heated under reflux for 3.5 hours. The cooled mixture was concentrated under reduced pressure and the solid residue partitioned between dichloromethane (30mL) and a solution of saturated sodium bicarbonate (1mL) in water (5mL), and the phases separated. The aqueous layer was extracted with dichloromethane (2x30mL), and the combined organic extracts dried (MgSO₄) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 95:5) to afford the title compound of example 31, 42mg.

¹H-nmr (CD₃OD, 400MHz) δ : 0.65 (m, 2H), 0.97 (m, 2H), 1.28 (d, 6H), 3.10 (m, 1H), 3.33 (s, 1H), 3.82 (s, 3H), 4.07 (m, 2H), 4.13 (t, 2H), 4.84 (s, 2H), 6.34 (d, 1H), 6.70 (d, 1H), 6.75 (s, 1H); LRMS : m/z (ES⁺) 380 [MH⁺]; Microanalysis found: C, 65.77; H, 6.69; N, 18.46. C₂₁H₂₅N₅O₂·0.2H₂O requires C, 65.84; H, 6.68; N, 18.28%.

Further elution gave the title compound of example 32, 40mg.

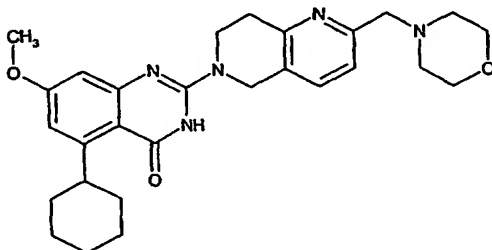
¹H-nmr (CD₃OD, 400MHz) δ : 0.62 (m, 2H), 0.97 (m, 2H), 1.56 (s, 6H), 3.29 (m, 1H), 3.82 (s, 3H), 4.00 (m, 2H), 4.53 (m, 2H), 4.84 (s, 2H), 6.34 (s, 1H), 6.70 (s, 1H), 6.75 (s, 1H); LRMS : m/z (ES⁺) 396 [MH⁺]; Microanalysis found: C, 63.12; H, 6.59; N, 17.21. C₂₁H₂₅N₅O₃·0.07CH₂Cl₂ requires C, 63.05; H, 6.31; N, 17.44%.

Example 335-Cyclobutyl-7-methoxy-2-(2-(4-morpholinylmethyl)-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone

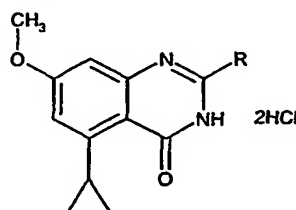
- 5 The title compound was obtained as a solid in 74% yield from the compounds from preparation 19 and 106, following the procedure described in example 4.
- ¹H-nmr (DMSO-d₆, 400MHz) δ : 1.66-1.75 (m, 1H), 1.83-2.03 (m, 3H), 2.29 (m, 2H), 2.38 (m, 4H), 2.93 (t, 2H), 3.51 (s, 2H), 3.56 (m, 4H), 3.81 (s, 3H), 3.92 (t, 2H), 4.57 (m, 1H), 4.77 (s, 2H), 6.59 (s, 2H), 7.27 (d, 1H), 7.57 (d, 1H), 11.05 (bs, 1H).
- 10 LRMS : m/z (ES⁺) 462 [MH⁺]
Microanalysis found: C, 67.66; H, 6.78; N, 14.95. C₂₆H₃₁N₅O₃ requires C, 67.66; H, 6.77; N, 15.17%.

Example 34

- 15 5-Cyclohexyl-7-methoxy-2-(2-(4-morpholinylmethyl)-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone

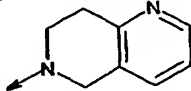
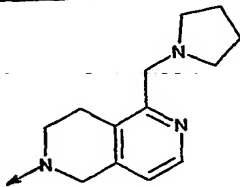
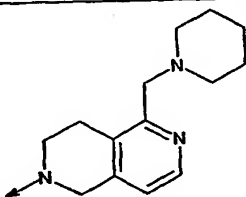


- The title compound was obtained as a solid in 70% yield, after recrystallisation from diethyl ether, from the compounds from preparation 20 and 106, following a similar procedure to that described in example 26.
- 20 ¹H-nmr (DMSO-d₆, 400MHz) δ : 1.15-1.46 (m, 5H), 1.66-1.84 (m, 5H), 2.38 (m, 4H), 2.94 (t, 2H), 3.52 (s, 2H), 3.57 (m, 4H), 3.79 (s, 3H), 3.93 (t, 2H), 4.14 (t, 1H), 4.77 (s, 2H), 6.57 (m, 2H), 7.27 (d, 1H), 7.57 (d, 1H), 11.03 (bs, 1H).
- LRMS : m/z (APCI⁺) 490 [MH⁺]
- 25 Microanalysis found: C, 68.84; H, 7.33; N, 14.18. C₂₈H₃₅N₅O₃ requires C, 68.69; H, 7.21; N, 14.30%.

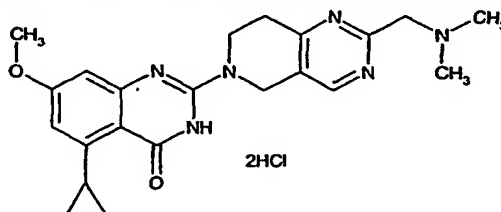
Examples 35 to 39

The following examples were prepared following the procedure described for examples 2 to 25. The compounds were then dissolved in a solution of dichloromethane with a minimum volume of methanol, then treated with 1N ethereal hydrochloric acid. The resultant mixture was evaporated under reduced pressure to afford the title compounds.

Ex. no.	R	Base	Yield% /Form	Spectroscopic and Analytical data
35		A	90	¹ H-nmr (DMSO-d ₆ , 400MHz) δ: 0.76 (m, 2H), 0.98 (m, 2H), 3.18-3.35 (m, 7H), 3.79 (s, 3H), 3.88 (s, 4H), 4.00 (m, 2H), 4.16 (s, 2H), 4.98 (s, 2H), 6.38 (s, 1H), 7.32 (bs, 2H), 7.46 (bs, 1H), 7.64 (bs, 1H), 11.47 (bs, 1H); LRMS (ES ⁺): m/z (MH ⁺) 447; Microanalysis: Found: C, 58.41; H, 6.57; N, 10.02. C ₂₆ H ₃₀ N ₄ O ₃ ·2HCl;H ₂ O requires C, 58.10; H, 6.38; N, 10.42%
36 (a)		A	56	¹ H-nmr (DMSO-d ₆ , 400MHz) δ: 0.74 (m, 2H), 0.98 (m, 2H), 3.10 (m, 2H), 3.22 (m, 3H), 3.32 (m, 1H), 3.80 (s, 3H), 3.92 (m, 1H), 4.00-4.44 (m, 9H), 5.02 (s, 2H), 6.38 (s, 1H), 7.33 (d, 1H), 7.45 (m, 2H), 11.50 (bs, 1H); LRMS (ES ⁺): m/z (MH ⁺) 447; Microanalysis: Found: C, 59.36; H, 6.28; N, 10.53. C ₂₆ H ₃₀ N ₄ O ₃ ·2HCl;0.4H ₂ O requires C, 59.29; H, 6.28; N, 10.64 %.

Ex. no.	R	Base	Yield % /Form	Spectroscopic and Analytical data
37 (b)		B	92	¹ H-nmr (DMSO-d ₆ , 400MHz) δ: 0.71 (m, 2H), 0.97 (m, 2H), 3.26 (t, 2H), 3.38 (m, 1H), 3.74 (s, 3H), 4.12 (t, 2H), 5.08 (s, 2H), 6.35 (s, 1H), 7.07 (bs, 1H), 7.75 (dd, 1H), 8.20 (m, 1H), 8.66 (d, 1H). LRMS m/z: (ES ⁻) 347 (M-H ⁻)
38 (a)		A	42 white solid	¹ H-nmr (DMSO-d ₆ , 400MHz) δ: 0.72 (m, 2H), 0.99 (m, 2H), 1.97 (m, 4H), 3.00 (m, 2H), 3.26-3.46 (m, 5H), 3.80 (s, 3H), 4.17 (m, 2H), 4.61 (s, 2H), 5.12 (s, 2H), 6.38 (s, 1H), 7.28 (bs, 1H), 7.57 (bs, 1H), 8.46 (d, 1H), 10.56 (bs, 1H). LRMS m/z : (ES ⁺) 432 (MH ⁺)
39		A	71 white solid	¹ H-nmr (DMSO-d ₆ , 400MHz) δ: 0.74 (m, 2H), 0.97 (m, 2H), 1.55 (m, 2H), 1.82 (m, 4H), 3.03 (t, 2H), 3.16-3.38 (m, 5H), 3.80 (s, 3H), 4.16 (t, 2H), 4.50 (s, 2H), 5.17 (s, 2H), 6.38 (s, 1H), 7.32 (d, 1H), 7.62 (bs, 1H), 8.49 (d, 1H), 10.04 (bs, 1H). LRMS m/z : (ES ⁺) 446 (MH ⁺) Microanalysis found: C, 58.21; H, 6.58; N, 13.05. C ₂₆ H ₃₁ N ₅ O ₂ ·2HCl·H ₂ O requires C, 58.32; H, 6.63; N, 12.79%.

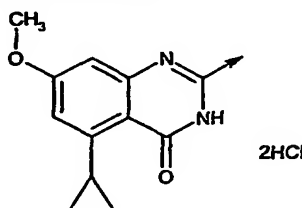
(b)-5,6,7,8-tetrahydro-1,6-naphthyridine (Chem. Pharm. Bull. 32, 2522, 1984) was used as the amine

Example 405-Cyclopropyl-2-(2-[(dimethylamino)methyl]-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-7-methoxy-4(3H)-quinazolinone dihydrochloride

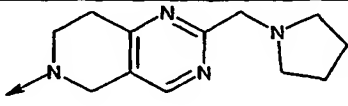
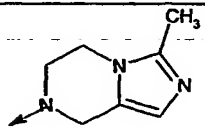
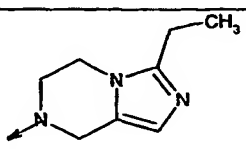
- 5 A mixture of the chloride from preparation 18 (60mg, 0.24mmol), the amine hydrochloride from preparation 121 (80mg, 0.30mmol) and diisopropylethylamine (258mg, 2mmol) in n-butanol (4mL) was heated under reflux for 1.5 hours. The cooled mixture was poured into water and extracted with dichloromethane (3x50mL). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure.
- 10 The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 80:20). The product was re-dissolved in dichloromethane treated with 1N ethereal hydrochloric acid (2mL), and the solution evaporated under reduced pressure to afford the title compound as a light brown solid, 60mg.
- 15 ¹H-nmr (DMSO-d₆ 400MHz) δ: 0.72 (m, 2H), 0.97 (m, 2H), 2.87 (s, 6H), 3.14 (m, 2H), 3.36 (m, 1H), 3.79 (s, 3H), 4.18 (m, 2H), 4.56 (s, 2H), 5.13 (s, 2H), 6.38 (s, 1H), 7.42 (bs, 1H), 8.71 (s, 1H), 10.49 (bs, 1H).
- LRMS : m/z (ES⁺) 407 [MH⁺]
- Microanalysis: Found: C, 54.11; H, 5.94; N, 16.83. C₂₂H₂₆N₆O₂·2HCl·0.5H₂O requires
- 20 C, 54.10 ; H, 5.98; N, 17.21 %

Examples 41 to 43

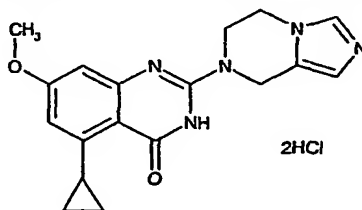
The following examples of general structure:



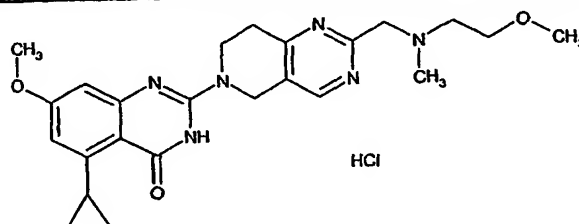
- 25 were prepared from the chloride from preparation 18, the appropriate amines and diisopropylethylamine, following a similar procedure to that described in example 40.

Ex. no.	R	Yield%/Form	Spectroscopic and Analytical data
41		63 off-white solid	$^1\text{H-nmr}$ (DMSO-d_6 , 400MHz) δ : 0.68 (m, 2H), 0.95 (m, 2H), 1.85-2.05 (m, 4H), 3.05 (t, 2H), 3.15 (m, 2H), 3.43 (m, 1H), 3.60 (m, 2H), 3.75 (s, 3H), 4.05 (m, 2H), 4.65 (d, 2H), 4.95 (s, 2H), 6.25 (s, 1H), 6.85 (bs, 1H), 8.73 (s, 1H), 10.45 (bs, 1H). LRMS : m/z (ES^+) 433 [MH^+]
42 (a)		86 white solid	$^1\text{H-nmr}$ (CD_3OD , 400MHz) δ : 0.77 (m, 2H), 1.07 (m, 2H), 2.66 (s, 3H), 3.10 (m, 1H), 3.91 (s, 3H), 4.34 (t, 2H), 4.43 (t, 2H), 5.16 (s, 2H), 6.64 (d, 1H), 7.11 (s, 1H), 7.46 (s, 1H). LRMS : m/z (ES^+) 352 [MH^+]. Microanalysis: Found: C, 54.19; H, 5.77; N, 16.28. $\text{C}_{19}\text{H}_{21}\text{N}_5\text{O}_2 \cdot 2\text{HCl}$ requires C, 53.78 ; H, 5.46; N, 16.50 %
43 (a)		78 yellow foam	$^1\text{H-nmr}$ (CD_3OD , 400MHz) δ : 0.78 (m, 2H), 1.09 (m, 2H), 1.41 (t, 3H), 3.04 (m, 3H), 3.92 (s, 3H), 4.35 (t, 2H), 4.46 (t, 2H), 5.18 (s, 2H), 6.65 (s, 1H), 7.12 (s, 1H), 7.49 (s, 1H). LRMS : m/z (ES^+) 366 [MH^+]. Microanalysis: Found: C, 53.58; H, 5.97; N, 15.27. $\text{C}_{20}\text{H}_{23}\text{N}_5\text{O}_2 \cdot 2\text{HCl}$ requires C, 53.48 ; H, 5.88; N, 15.59 %

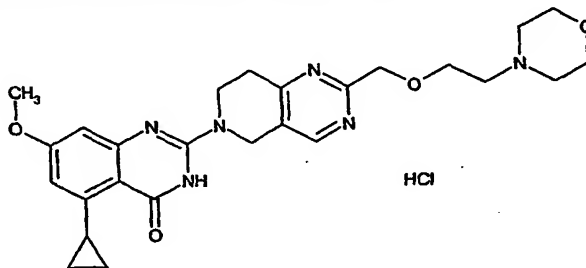
(a)-triethylamine was used instead of diisopropylethylamine

Example 445-Cyclopropyl-2-(5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)-7-methoxy-4(3H)-quinazolinone dihydrochloride

- 5 A mixture of the chloride from preparation 18 (70mg, 0.28mmol), the amine hydrochloride from preparation 129 (66mg, 0.34mmol) and triethylamine (113μl, 1.12mmol) in n-butanol (6mL) was heated under reflux for 6 hours. The cooled mixture was concentrated under reduced pressure and the residual solid partitioned between water (5mL) and dichloromethane:methanol (95:5, 50mL) and the layers separated.
- 10 The aqueous phase was extracted with dichloromethane:methanol (95:5, 2x30mL), and the combined organic solutions dried (MgSO₄) and evaporated under reduced pressure. The product was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (98:2 to 90:10) to give a white solid. This was suspended in water, diluted with saturated sodium bicarbonate solution, and
- 15 extracted with dichloromethane (3x50mL). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure. The solid was dissolved in dichloromethane:methanol (1:1, 8mL), 1N ethereal hydrochloric acid added, and the mixture evaporated under reduced pressure to afford the title compound as a foam, 69mg.
- 20 ¹H-nmr (DMSO-d₆, 400MHz) δ: 0.74 (m, 2H), 0.99 (m, 2H), 3.25 (m, 1H), 3.81 (s, 3H), 4.20 (t, 2H), 4.46 (t, 2H), 5.10 (s, 2H), 6.42 (s, 1H), 7.01 (s, 1H), 7.64 (s, 1H), 9.15 (s, 1H).
- LRMS : m/z (ES⁺) 338 [MH⁺]
- Microanalysis found: C, 52.78; H, 5.46; N, 16.82. C₁₈H₁₉N₅O₂·2HCl requires C, 52.69;
- 25 H, 5.16; N, 17.07%.

Example 455-Cyclopropyl-7-methoxy-2-(2-((2-methoxyethyl)(methyl)amino)methyl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-4(3H)-quinazolinone hydrochloride

- 5 A mixture of the chloride from preparation 18 (140mg, 0.5mmol), the amine hydrochloride from preparation 122 (290mg, 0.84mmol) and triethylamine (390μl, 2.8mmol) in n-butanol (3mL) was heated under reflux for 1.5 hours. The cooled mixture was filtered, the resulting solid washed with n-butanol and diethyl ether, then dried at 60°C *in vacuo*, to afford the title compound as a cream solid.
- 10 ¹H-nmr (CDCl₃, 400MHz) δ: 0.73 (m, 2H), 0.97 (m, 2H), 2.41 (s, 3H), 2.75 (t, 2H), 3.08 (t, 2H), 3.33 (s, 3H), 3.38 (m, 1H), 3.56 (t, 2H), 3.86 (m, 5H), 4.10 (t, 2H), 4.92 (s, 2H), 6.33 (s, 1H), 6.68 (s, 1H), 8.51 (s, 1H), 11.12 (bs, 1H).
- LRMS : m/z (ES⁻) 449 [M-H]⁻
- Microanalysis found: C, 58.44; H, 6.16; N, 16.97. C₂₄H₃₀N₆O₃·HCl;0.3H₂O requires C, 58.54; H, 6.47; N, 17.07%.
- 15

Example 465-Cyclopropyl-7-methoxy-2-(2-(4-morpholinyl)ethoxy)methyl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-4(3H)-quinazolinone hydrochloride

20

The title compound was obtained as a cream solid in 65% yield, from the chloride from preparation 18 and the amine hydrochloride from preparation 125, following a similar procedure to that described in example 45, except, diisopropylethylamine was used instead of triethylamine.

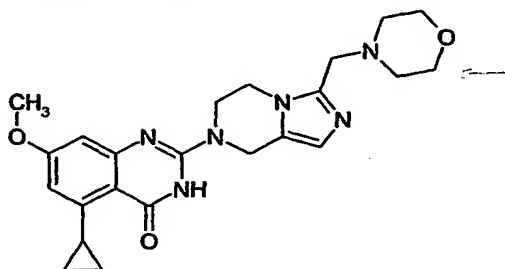
¹H-nmr (CDCl₃, 400MHz) δ: 0.85 (m, 2H), 00.97 (m, 2H), 2.50 (m, 4H), 2.67 (m, 2H), 3.09 (m, 2H), 3.38 (m, 1H), 3.65 (m, 4H), 3.74 (t, 2H), 3.83 (s, 3H), 4.15 (m, 2H), 4.72 (s, 2H), 4.91 (s, 2H), 6.35 (s, 1H), 6.64 (s, 1H), 8.53 (s, 1H), 10.88 (bs, 1H).

LRMS : m/z (ES⁻) 491 [M-H]

- 5 Microanalysis found: C, 58.71; H, 6.15; N, 15.65. C₂₆H₃₂N₆O₄·HCl requires C, 59.03; H, 6.29; N, 15.89%.

Example 47

10 5-Cyclopropyl-7-methoxy-2-(3-morpholin-4-ylmethyl-5,6-dihydro-8H-imidazo[1,5-a]pyrazin-7-yl)-3H-quinazolin-4-one



- 15 The chloro compound from preparation 18 (100 mg, 0.4 mmol) was mixed with the imidazopyrazine from preparation 173 (106 mg, 0.48 mmol) and triethylamine (167 μl, 1.2 mmol) in n-butanol (10 ml) under a nitrogen atmosphere and the mixture was heated under reflux for 6 hours. The reaction mixture was cooled to room temperature and the solid formed was isolated by filtration. The material obtained was washed with n-butanol (20 ml), diethyl ether (100 ml), water (20 ml) and diethyl ether (100 ml) and was then dried under vacuum at 80°C for 4 hours to give the title compound (95 mg).

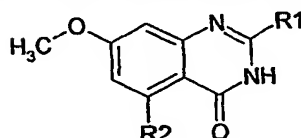
- 20 ¹H-nmr (DMSO-d₆ 400MHz) δ: 1.65 (m, 2H), 1.94 (m, 2H), 2.34 (m, 4H), 3.53 (m, 7H), 3.78 (s, 3H), 3.98 (m, 2H), 4.12 (m, 2H), 4.80 (s, 2H), 6.19 (d, 1H), 6.57 (d, 1H), 6.59 (s, 1H), 11.20 (s, 1H)

LRMS: m/z (ES⁺) 459 [MNa⁺]

Microanalysis found: C, 62.38; H, 6.39; N, 18.95; C₂₃H₂₈N₆O₃ · 0.25 H₂O requires C, 62.29; H, 6.47; N, 19.25%

Examples 48 to 86

The compounds of the following tabulated examples of the general formula:



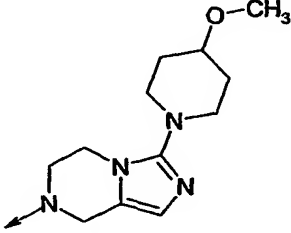

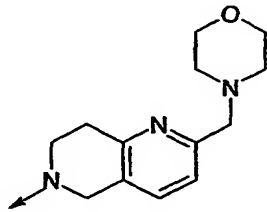

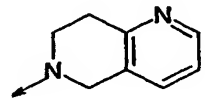
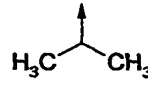
were prepared by the general method outlined below using the appropriate chloro compound and cyclic amine.

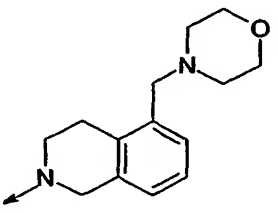
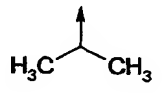
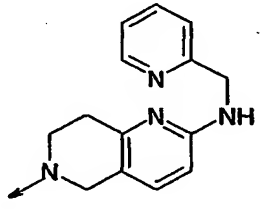
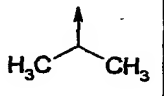
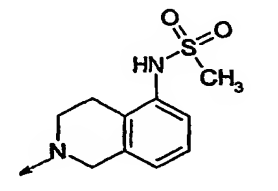
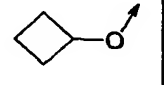
To a solution of the chloro-quinazolinone (1eq) in n-butanol (15ml per mmol) under nitrogen was added N,N-diisopropylethylamine or triethylamine (1.7-8eq) and the appropriate secondary amine (1-2eq). The resultant mixture was then heated under reflux for 1-6 hours, cooled and the product was isolated by filtration, washing with n-butanol and diethyl ether (Method a).

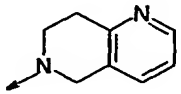
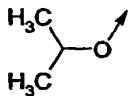
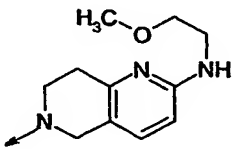
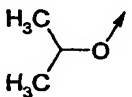
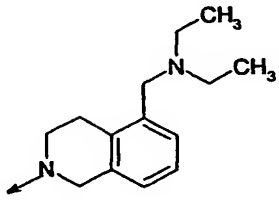
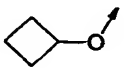
Some reaction mixtures were concentrated under reduced pressure, the residue partitioned between dichloromethane and water, the organic phase separated, dried (MgSO₄) and evaporated under reduced pressure (Method b).

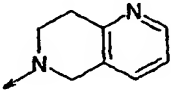
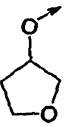
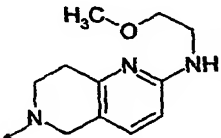
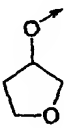
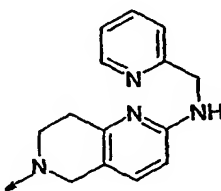
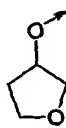
Some products were additionally purified by column chromatography on silica gel using dichloromethane: methanol or dichloromethane: methanol: 0.88 ammonia as eluants (Method c).

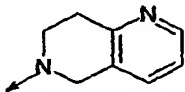
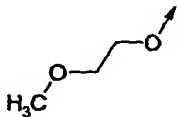
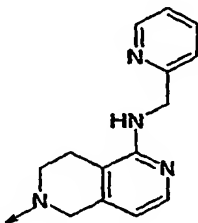
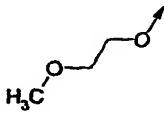
Ex No. (Method)	R1	R2	Yield %	Spectroscopic and analytical data
48 (b)			79	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 0.66 (m, 2H), 0.94 (m, 2H), 0.35 (m, 1H), 3.77 (s, 3H), 3.99 (m, 2H), 4.12 (m, 2H), 4.42 (d, 2H), 4.82 (s, 2H), 5.16 (t, 1H), 6.18 (s, 1H), 6.56 (s, 1H), 6.68 (s, 1H). LRMS: m/z (ES ⁺) 390 [MNa ⁺] Microanalysis found: C, 61.32; H, 5.76; N, 18.48; C ₁₉ H ₂₁ N ₅ O ₃ 0.25 H ₂ O requires; C, 61.36; H, 5.83; 18.83%

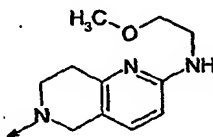
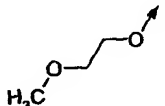
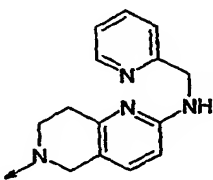
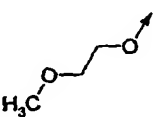
Ex No. (Method)	R1	R2	Yield %	Spectroscopic and analytical data
49 ^D (a)			58	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 0.66 (m, 2H), 0.95 (m, 2H), 1.56 (m, 2H), 1.90 (m, 2H), 2.79 (m, 2H), 3.15 (m, 2H), 3.25 (s, 3H), 3.30 (m, 1H), 3.50 (m, 1H), 3.77 (s, 3H), 3.86 (m, 2H), 3.93 (m, 2H), 4.76 (s, 2H), 6.16 (s, 1H), 6.47 (s, 1H), 6.54 (s, 1H), 11.10 (s, 1H); LRMS: m/z (ES ⁺) 451 [MH ⁺]; Microanalysis found: C, 63.65; 6.76; 18.40; C ₂₄ H ₃₀ N ₆ O ₃ 0.1 H ₂ O requires; C, 63.73; H, 6.73; N 18.58%
50 ^D (a)			74	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 1.73 (m, 1H), 1.96 (m, 3H), 2.29 (s, m, 2H), 2.38 (m, 4H), 2.93 (t, 2H), 3.51 (s, 2H), 3.56 (m, 4H), 3.80 (s, 3H), 3.92 (t, 2H), 4.51 (m, 1H), 4.77 (s, 2H), 6.59 (s, 2H), 7.27 (d, 1H), 7.57 (d, 1H), 11.05 (s, 1H); LRMS: m/z (ES ⁺) 485 [MNa ⁺]
51 ^D (a)			41	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 1.15 (d, 6H), 2.98 (t, 2H), 3.80 (s, 3H), 3.94 (t, 2H), 4.53 (m, 1H), 4.80 (s, 2H), 6.60 (s, 2H), 7.20 (m, 1H), 7.60 (d, 1H), 8.38 (d, 1H), 10.91 (s, 1H); LRMS: m/z (ES ⁺) 451 [MH ⁺]; Microanalysis: Found: C, 68.42; H, 6.50; N, 15.66; C ₂₀ H ₂₂ N ₄ O ₂ requires; C, 68.55; H, 6.33; N, 15.99%. M.p. 227-229°C

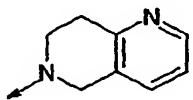
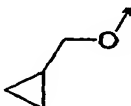
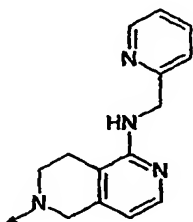
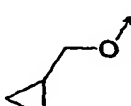
Ex No. (Method)	R1	R2	Yield %	Spectroscopic and analytical data
52 ^D (a)			58	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 1.16 (d, 6H), 2.33 (m, 4H), 2.95 (t, 2H), 3.42 (s, 2H), 3.52 (m, 4H), 3.79 (s, 3H), 3.83 (t, 2H), 4.55 (m, 1H), 4.78 (s, 2H), 6.58 (s, 2H), 7.10 (m, 3H). LRMS: m/z (ES ⁺) 449 [MH ⁺]. Microanalysis: Found: C, 69.62; H, 7.31; N, 12.19; C ₂₆ H ₃₂ N ₄ O ₃ requires; C, 69.62; H, 7.19; 12.49%. M.p. 231-233°C
53 ^D (a)			62	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 1.16 (d, 6H), 2.71 (t, 2H), 3.80 (s, 3H), 3.86 (t, 2H), 4.54 (m, 5H), 6.40 (d, 1H), 6.58 (d, 2H), 6.81 (s, 1H), 7.19 (m, 2H), 7.30 (d, 1H), 7.67 (m, 1H), 8.48 (d, 1H), 10.84 (s, 1H). LRMS: m/z (ES ⁺) 457 [MH ⁺]. Microanalysis: Found: C, 68.21; H, 6.21; 18.21; C ₂₆ H ₂₈ N ₆ O ₂ requires C, 68.40; H, 6.18; N, 18.41% M.p. 227-229°C
54 ¹ (a)			60	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 1.62 (m, 1H), 1.79 (m, 1H), 2.08 (m, 2H), 2.41 (m, 2H), 2.90 (t, 2H), 2.99 (s, 3H), 3.79 (m, 5H), 4.67 (m, 1H), 4.76 (s, 2H), 5.95 (d, 1H), 6.30 (s, 1H), 7.11 (d, 1H), 7.20 (m, 2H). LRMS: m/z (ES ⁺) 471 [MH ⁺]

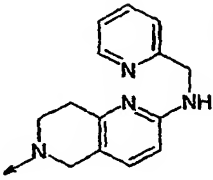
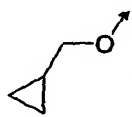
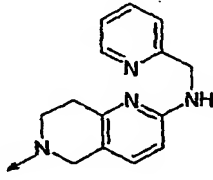
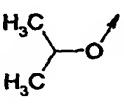
Ex No. (Method)	R1	R2	Yield %	Spectroscopic and analytical data
55 (b)			68	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 1.27 (d, 6H), 2.95 (s, 2H), 3.80 (s, 3H), 3.92 (s, 2H), 4.54 (m, 1H), 4.80 (s, 2H), 6.20 (s, 1H), 6.35 (s, 1H), 7.20 (m, 1H), 7.59 (d, 1H), 8.39 (s, 1H). LRMS: m/z (ES ⁺) 367 [MH ⁺]. Microanalysis: Found: C, 64.63; H, 5.99; N, 15.01; C ₂₀ H ₂₂ N ₄ O ₃ 0.25H ₂ O requires; C, 64.76; H, 6.11; N, 15.10%
56 (a)			81	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 1.27 (d, 6H), 2.72 (t, 2H), 3.27 (s, 3H), 3.39 (t, 2H), 3.44 (m, 2H), 3.79 (s, 3H), 3.85 (t, 2H), 4.54 (m, 3H), 6.18 (s, 1H), 6.21 (s, 1H), 6.32 (s, 1H), 6.39 (d, 1H), 7.18 (d, 1H), 10.60 (s, 1H). LRMS: m/z (ES ⁺) 440 [MH ⁺]. Microanalysis: Found: C, 61.80; H, 6.62; N, 15.31; C ₂₃ H ₂₉ N ₅ O ₄ 0.4H ₂ O requires C, 61.84; H, 6.72; N, 15.68%
57 ² (a)			34	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 0.95 (t, 6H), 1.65 (m, 1H), 1.79 (m, 1H), 2.09 (m, 2H), 2.44 (m, 6H), 3.93 (t, 2H), 3.48 (s, 2H), 3.80 (m, 2H), 4.69 (t, 2H), 4.77 (s, 2H), 5.92 (d, 1H), 6.29 (d, 1H), 7.10 (m, 3H). LRMS: m/z (ES ⁺) 463 [MH ⁺]

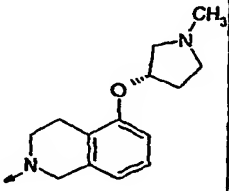

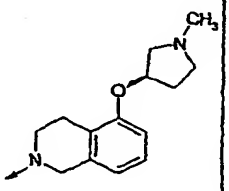

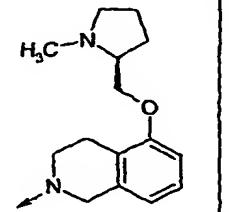

Ex No. (Method)	R1	R2	Yield %	Spectroscopic and analytical data
58 (a)			65	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 2.01 (m, 1H), 2.17 (m, 1H), 2.96 (t, 2H), 3.83 (m, 9H), 4.79 (s, 2H), 4.99 (m, 1H), 6.14 (s, 1H), 6.25 (s, 1H), 7.20 (m, 1H), 7.60 (d, 1H), 8.38 (d, 1H), 10.70 (s, 1H) LRMS: m/z (ES ⁺) 417 [MNa ⁺] Microanalysis: Found: C, 63.10; H, 5.72; N, 13.66; C ₂₁ H ₂₂ N ₄ O ₄ 0.25H ₂ O requires; C, 63.23; H, 5.68; N, 14.04%
59 (a)			82	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 2.02 (m, 1H), 2.14 (m, 1H), 2.72 (t, 2H), 3.26 (s, 3H), 3.38 (m, 2H), 3.42 (m, 2H), 3.85 (m, 9H), 4.56 (s, 2H), 4.99 (m, 1H), 6.12 (s, 1H), 6.21 (s, 1H), 6.36 (m, 2H), 7.18 (d, 1H), 10.67 (s, 1H). LRMS: m/z (ES ⁺) 490 [MNa ⁺] Microanalysis: Found: C, 61.05; H, 6.21; N, 14.68; C ₂₄ H ₂₉ N ₅ O ₅ 0.25H ₂ O requires; C, 61.07; H, 6.30; N, 14.84%
60 (a)			84	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 2.01 (m, 1H), 2.15 (m, 1H), 2.70 (m, 2H), 3.82 (m, 9H), 4.53 (d, 2H), 4.59 (s, 2H), 4.99 (m, 1H), 6.12 (s, 1H), 6.23 (s, 1H), 6.41 (d, 1H), 6.83 (s, 1H), 7.20 (m, 2H), 7.32 (d, 1H), 7.68 (m, 1H), 8.47 (d, 1H), 10.55 (s, 1H). LRMS: m/z (ES ⁺) 501 [MH ⁺]. Microanalysis: Found: C, 63.97; H, 5.68; N, 16.28; C ₂₇ H ₂₈ N ₆ O ₄ 0.4 H ₂ O requires; C63.87; H, 5.68; N, 16.55%

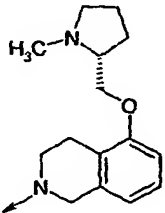

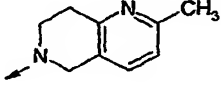

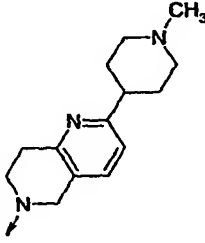

Ex No. (Method)	R1	R2	Yield %	Spectroscopic and analytical data
61 ^D (a)			71	<p>¹H-NMR (DMSO-d₆, 400 MHz) δ: 2.96 (t, 2H), 3.36 (s, 3H), 3.68 (t, 2H), 3.79 (s, 3H), 3.94 (t, 2H), 4.09 (t, 2H), 4.80 (s, 2H), 6.20 (d, 1H), 6.32 (s, 1H), 7.20 (m, 1H), 7.60 (d, 1H), 8.38 (d, 1H). LRMS: m/z (ES⁺) 383 [MH⁺].</p> <p>Microanalysis: Found: C, 61.94; H, 5.80; N, 14.16; C₂₀H₂₂N₄O₄ 0.3 H₂O requires; C, 61.85; H, 5.88; N, 14.43%</p>
62 ^D (a)			89	<p>¹H-NMR (DMSO-d₆, 400 MHz) δ: 2.60 (m, 2H), 3.37 (s, 3H), 3.68 (m, 2H), 3.80 (s, 3H), 3.92 (m, 2H), 4.09 (m, 2H), 4.66 (s, 4H), 6.20 (s, 1H), 6.33 (s, 1H), 6.40 (d, 1H), 6.54 (m, 1H), 7.15 (m, 1H), 7.23 (m, 1H), 7.63 (m, 1H), 6.75 (d, 1H), 8.46 (d, 1H). LRMS: m/z (ES⁺) 489 [MH⁺]. Microanalysis: Found: C, 63.41; H, 5.89; N, 16.67; C₂₆H₂₈N₆O₄ 0.25H₂O requires; C, 63.34; H, 5.83; N, 17.04%</p> <p>M.p. 216-218°C</p>

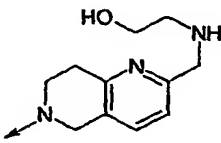

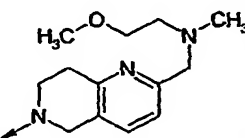

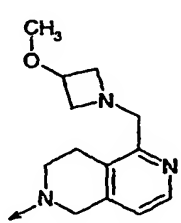

Ex No. (Method)	R1	R2	Yield %	Spectroscopic and analytical data
63 ^D (c)			74	<p>¹H-NMR (DMSO-d₆, 400 MHz) δ: 2.72 (t, 2H), 3.26 (s, 3H), 3.38 (m, 5H), 3.41 (m, 2H), 3.68 (t, 2H), 3.80 (s, 3H), 3.85 (t, 2H), 4.09 (t, 2H), 4.55 (s, 2H), 6.19 (s, 1H), 6.32 (s, 1H), 6.36 (d, 2H), 7.15 (d, 1H)</p> <p>LRMS: m/z (ES⁺) 456 [MH⁺] Microanalysis: Found: C, 60.44; H, 6.42; N, 15.27; C₂₃H₂₉N₅O₅ requires; C, 60.65; H, 6.42; N, 15.37%</p>
64 ^D (a)			92	<p>¹H-NMR (DMSO-d₆, 400 MHz) δ: 2.69 (t, 2H), 3.35 (s, 3H), 3.69 (t, 2H), 3.80 (s, 3H), 3.84 (t, 2H), 4.09 (t, 2H), 4.53 (d, 2H), 4.58 (s, 2H), 6.19 (s, 1H), 6.32 (s, 1H), 6.41 (d, 1H), 6.83 (t, 1H), 7.20 (m, 2H), 7.31 (d, 1H), 7.69 (m, 1H), 8.48 (d, 1H)</p> <p>LRMS: m/z (ES⁺) 489 [MH⁺] Microanalysis: Found: C, 63.35; H, 5.83; N, 17.84; C₂₆H₂₈N₆O₄ 0.25H₂O requires; C, 63.34; H, 5.83; N, 17.04%</p>

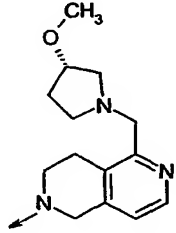

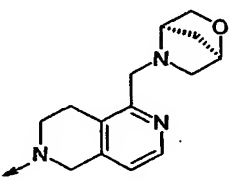

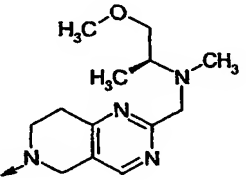

Ex No. (Method)	R1	R2	Yield %	Spectroscopic and analytical data
65 ^D (a)			75	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 0.40 (m, 2H), 0.52 (m, 2H), 1.21 (m, 1H), 2.95 (t, 2H), 3.79 (s, 3H), 3.88 (d, 2H), 3.92 (t, 2H), 4.79 (s, 2H), 6.18 (s, 1H), 6.31 (s, 1H), 7.20 (m, 1H), 7.60 (d, 1H), 8.35 (d, 1H), 10.75 (s, 1H). LRMS: m/z (ES ⁺) 379 [MH ⁺]. Microanalysis: Found: C, 66.34; H, 5.91; N, 14.60; C ₂₁ H ₂₂ N ₄ O ₃ requires; C, 66.65; H, 5.86; N, 14.80%. M.p. 191-193°C
66 ^D (a)			76	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 0.39 (d, 2H), 0.52 (d, 2H), 1.22 (m, 1H), 2.60 (m, 2H), 3.79 (s, 3H), 3.89 (d, 2H), 3.92 (m, 2H), 4.66 (s, 4H), 6.17 (s, 1H), 6.32 (s, 1H), 6.39 (d, 1H), 6.52 (m, 1H), 7.18 (m, 1H), 7.22 (m, 1H), 7.63 (m, 1H), 7.74 (d, 1H), 8.46 (d, 1H). LRMS: m/z (ES ⁺) 485 [MH ⁺]. Microanalysis: Found: C, 65.29; H, 5.96; N, 16.83; C ₂₇ H ₂₈ N ₆ O ₃ 0.67H ₂ O requires; C, 65.30; H, 5.95; N, 16.92%. M.p. 160-162°C

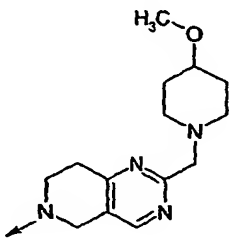

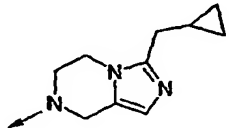

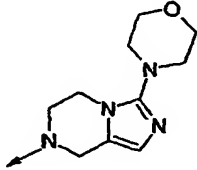

Ex No. (Method)	R1	R2	Yield %	Spectroscopic and analytical data
67 (a)			86	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 0.38 (d, 2H), 0.32 (d, 2H), 1.20 (m, 1H), 2.69 (t, 2H), 3.77 (s, 3H), 3.83 (m, 4H), 4.52 (d, 2H), 4.56 (s, 2H), 6.14 (s, 1H), 6.29 (s, 1H), 6.40 (d, 1H), 6.79 (t, 1H), 7.19 (d, 2H), 7.30 (d, 1H), 7.68 (m, 1H), 7.47 (d, 1H). LRMS: m/z (ES ⁺) 485 [MH ⁺] Microanalysis: Found: C, 66.60; H, 5.99; N, 16.93; C ₂₇ H ₂₈ N ₆ O ₃ requires; C, 66.93; H, 5.82; N, 17.34%. M.p. 204-206°C
68 (a)			86	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 1.28 (d, 6H), 2.72 (s, 2H), 3.79 (s, 3H), 3.83 (t, 2H), 4.54 (m, 5H), 6.15 (s, 1H), 6.33 (s, 1H), 6.20 (d, 1H), 6.85 (s, 1H), 7.20 (d, 2H), 7.32 (d, 1H), 7.70 (m, 1H), 8.49 (s, 1H), 10.63 (s, 1H). LRMS: m/z (ES ⁺) 473 [MH ⁺]. Microanalysis: Found: C, 65.27; H, 6.07; N, 17.30; C ₂₆ H ₂₈ N ₆ O ₃ 0.3H ₂ O requires; C, 65.34; H, 6.03; N, 17.58%. M.p. 234-236°C

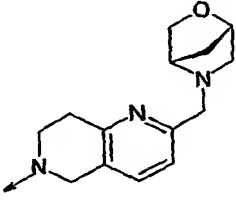

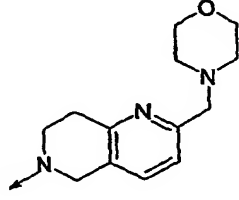
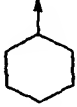
Ex No. (Method)	R1	R2	Yield %	Spectroscopic and analytical data
69 ^D (c)			39	¹ Hnmr (DMSO-d ₆ , 400MHz) δ: 0.64 (m, 2H), 0.92 (m, 2H), 1.76 (m, 1H), 2.28 (m, 4H), 2.40 (m, 1H), 2.62 (m, 2H), 2.70 (m, 2H), 2.80 (m, 1H), 3.50 (m, 1H), 3.76 (s, 3H), 3.83 (t, 2H), 4.73 (s, 2H), 4.84 (m, 1H), 6.13 (s, 1H), 6.52 (s, 1H), 6.74 (m, 2H), 7.12 (dd, 1H), 11.00 (s, 1H). LRMS: m/z (ES ⁺) 447 [MH ⁺] Microanalysis found: C, 68.72; H, 6.76; N, 12.22. C ₂₆ H ₃₀ N ₄ O ₃ ; 0.4H ₂ O requires; C, 68.82; H, 6.84; N, 12.35%.
70 ^D (c)			8	¹ Hnmr (DMSO-d ₆ , 400MHz) δ: 0.61 (m, 2H), 0.88 (m, 2H), 1.76 (m, 1H), 2.24 (m, 4H), 2.27 (s, 3H), 2.40 (m, 1H), 2.62 (m, 2H), 2.67 (m, 2H), 2.82 (m, 1H), 3.46 (m, 1H), 3.73 (s, 3H), 3.79 (t, 2H), 4.70 (s, 2H), 4.82 (m, 1H), 6.13 (s, 1H), 6.52 (s, 1H), 6.71 (m, 2H), 7.09 (dd, 1H), 11.00 (s, 1H). LRMS: m/z (ES ⁺) 447 [MH ⁺] Microanalysis found: C, 68.40; H, 6.85; N, 12.19. C ₂₆ H ₃₀ N ₄ O ₃ ; 0.5H ₂ O requires; C, 68.55; H, 6.86; N, 12.30%.
71 ^D (a)			84	¹ Hnmr (DMSO-d ₆ , 400MHz) δ: 0.65 (m, 2H), 0.93 (m, 2H), 1.60 (m, 1H), 1.68 (m, 2H), 1.95 (m, 1H), 2.20 (m, 1H), 2.38 (s, 3H), 2.60 (m, 1H), 2.73 (m, 2H), 2.96 (m, 1H), 3.49 (m, 1H), 3.76 (s, 3H), 3.83 (m, 3H), 3.94 (m, 1H), 4.75 (s, 2H), 6.14 (s, 1H), 6.52 (s, 1H), 6.78 (m, 2H), 7.14 (dd, 1H), 11.00 (s, 1H). LRMS: m/z (ES ⁺) 461 [MH ⁺]. Microanalysis found: C, 70.30; H, 7.04; N, 12.09. C ₂₇ H ₃₂ N ₄ O ₃ requires; C, 70.41; H, 7.00; N, 12.16%.

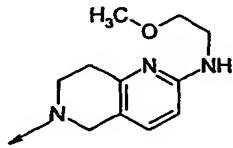
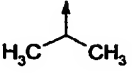
Ex No. (Method)	R1	R2	Yield %	Spectroscopic and analytical data
72 ^D (a)			73	¹ Hnmr (DMSO-d ₆ , 400MHz) δ: 0.63 (m, 2H), 0.92 (m, 2H), 1.60 (m, 1H), 1.67 (m, 2H), 1.95 (m, 1H), 2.20 (m, 1H), 2.37 (s, 3H), 2.60 (m, 1H), 2.72 (t, 2H), 2.95 (m, 1H), 3.49 (m, 1H), 3.75 (s, 3H), 3.82 (m, 3H), 3.94 (m, 1H), 4.73 (s, 2H), 6.12 (s, 1H), 6.51 (s, 1H), 6.78 (m, 2H), 7.12 (dd, 1H), 10.97 (s, 1H). LRMS: m/z (ES ⁺) 459 [M-H]. Microanalysis found: C, 69.80; H, 7.07; N, 12.01. C ₂₇ H ₃₂ N ₄ O ₃ ; 0.25H ₂ O requires; C, 69.73; H, 7.04; N, 12.05%.
73 ^{D,3} (b)			87	¹ Hnmr (DMSO-d ₆ , 400MHz) δ: 0.64 (m, 2H), 0.95 (m, 2H), 2.40 (s, 3H), 2.92 (t, 2H), 3.50 (m, 1H), 3.78 (s, 3H), 3.95 (t, 2H), 4.78 (s, 2H), 6.17 (s, 1H), 6.56 (s, 1H), 7.07 (d, 1H), 7.50 (d, 1H), 11.12 (s, 1H). LRMS: m/z (ES ⁺) 363 [MH ⁺]. Microanalysis found: C, 66.98; H, 6.07; N, 14.70. C ₂₁ H ₂₂ N ₄ O ₂ ; 0.70H ₂ O requires; C, 67.25; H, 6.29; N, 14.94%.
74 (b)			95	¹ Hnmr (CDCl ₃ , 400MHz) δ: 0.71 (m, 2H), 0.97 (m, 2H), 1.80-2.00 (m, 4H), 2.07 (m, 2H), 2.33 (s, 3H), 3.00 (m, 1H), 3.10 (t, 2H), 3.39 (m, 1H), 3.85 (s, 3H), 4.02 (t, 2H), 4.84 (s, 2H), 6.29 (s, 1H), 6.65 (s, 1H), 7.07 (d, 1H), 7.40 (d, 1H), 10.03 (m, 1H). LRMS: m/z (ES ⁺) 447 [MH ⁺]. Microanalysis found: C, 67.44; H, 6.96; N, 14.92. C ₂₆ H ₃₁ N ₅ O ₂ ; 0.25CH ₂ Cl ₂ requires; C, 67.54; H, 6.80; N, 15.00%.

Ex No. (Method)	R1	R2	Yield %	Spectroscopic and analytical data
75 ^D (b)			35	¹ Hnmr (DMSO-d ₆ , 400MHz) δ: 0.65 (m, 2H), 0.95 (m, 2H), 2.61 (t, 2H), 2.94 (t, 2H), 3.50 (m, 3H), 3.75 (s, 2H), 3.78 (s, 3H), 3.95 (t, 2H), 4.48 (m, 1H), 4.78 (s, 2H), 6.15 (s, 1H), 6.53 (s, 1H), 7.25 (d, 1H), 7.57 (d, 1H). Microanalysis found: C, 64.10; H, 6.49; N, 16.10. C ₂₃ H ₂₇ N ₅ O ₃ ; 0.5H ₂ O requires; C, 65.54; H, 6.46; N, 16.62%.
76 ^D (b)			16	¹ Hnmr (CDCl ₃ , 400MHz) δ: 0.75 (m, 2H), 0.99 (m, 2H), 2.37 (bs, 3H), 2.68 (m, 2H), 3.14 (t, 2H), 3.36 (s, 3H), 3.39 (m, 1H), 3.57 (m, 2H), 3.73 (m, 2H), 3.84 (s, 3H), 4.03 (t, 2H), 4.88 (s, 2H), 6.30 (s, 1H), 6.68 (s, 1H), 7.38 (m, 1H), 7.45 (d, 1H), 10.37 (bs, 1H). LRMS: m/z (ES ⁺) 472 [MNa ⁺]. Microanalysis found: C, 65.82; H, 7.06; N, 15.01. C ₂₅ H ₃₁ N ₅ O ₃ ; 0.3H ₂ O requires; C, 66.00; H, 7.00; N, 15.39%.
77 ^D (b)			30	¹ Hnmr (CDCl ₃ , 400MHz) δ: 0.75 (m, 2H), 1.00 (m, 2H), 3.05 (m, 2H), 3.28 (s, 3H), 3.40 (m, 1H), 3.64 (m, 1H), 3.83 (s, 3H), 3.97 (m, 2H), 4.14 (m, 2H), 4.24 (m, 2H), 4.83 (s, 2H), 6.33 (d, 1H), 6.65 (s, 1H), 7.06 (d, 1H), 8.38 (d, 1H). LRMS: m/z (ES ⁺) 448.8 [MH ⁺]. Microanalysis found: C, 65.15; H, 6.56; N, 14.92. C ₂₅ H ₂₉ N ₅ O ₃ ; 0.75H ₂ O requires; C, 65.13; H, 6.67; N, 15.19%.

Ex No. (Method)	R1	R2	Yield %	Spectroscopic and analytical data
78 ^D (b)			26	¹ Hnmr (CDCl ₃ , 400MHz) δ: 0.78 (m, 2H), 1.01 (m, 2H), 2.22 (m, 2H), 3.18 (m, 2H), 3.37 (s, 3H), 3.40 (m, 2H), 3.84 (s, 3H), 4.02 (m, 3H), 4.21 (m, 1H), 4.90 (s, 2H), 6.32 (s, 1H), 6.65 (s, 1H), 7.10 (d, 1H), 8.38 (d, 1H). LRMS: m/z (ES ⁺) 462.9 [MH ⁺]. Microanalysis found: C, 63.38; H, 6.60; N, 14.15. C ₂₆ H ₃₁ N ₅ O ₃ ; 0.45 CH ₂ Cl ₂ requires C, 63.56; H, 6.94; N, 14.01%.
79 (a)			51	¹ Hnmr (DMSOd ₆ , 400MHz) δ: 0.55 (m, 2H), 0.93 (m, 2H), 1.55 (m, 1H), 1.75 (m, 1H), 2.72 (m, 1H), 3.00 (m, 1H), 3.28-3.38 (m, 4H), 3.50 (m, 2H), 3.76 (m, 5H), 3.90 (m, 2H), 4.28 (s, 1H), 4.80 (s, 2H), 6.18 (d, 1H), 6.56 (d, 1H), 7.13 (d, 1H), 8.24 (d, 1H), 11.09 (s, 1H). LRMS: m/z (ES ⁺) 460 [MH ⁺]. Microanalysis found: C, 67.26; H, 6.42; N, 15.02. C ₂₆ H ₂₉ N ₅ O ₃ ; 0.25H ₂ O requires; C, 67.96; H, 6.36; N, 15.24%.
80 (a)				¹ Hnmr (CDCl ₃ , 400MHz) δ: 0.68 (m, 2H), 0.95 (m, 2H), 1.03 (d, 3H), 2.32 (s, 3H), 2.98 (m, 1H), 3.02 (t, 2H), 3.26 (m, 5H), 3.50 (m, 1H), 3.80 (s, 3H), 3.82 (s, 2H), 2.99 (t, 2H), 4.83 (s, 2H), 6.27 (d, 1H), 6.62 (d, 1H), 8.48 (s, 1H). LRMS: m/z (ES ⁺) 487 [MNa ⁺]

Ex No. (Method)	R1	R2	Yield %	Spectroscopic and analytical data
81 (a)				¹ Hnmr (DMSOd ₆ + TFAd, 400MHz) δ: 0.78 (m, 2H), 1.02 (m, 2H), 1.18 (m, 4H), 3.07 (m, 4H), 3.17 (t, 2H), 3.22 (s, 3H), 3.30 (m, 1H), 3.54 (m, 1H), 3.82 (s, 3H), 4.12 (t, 2H), 4.60 (m, 2H), 5.03 (s, 2H), 6.44 (s, 1H), 7.08 (s, 1H), 8.76 (s, 1H). LRMS: m/z (ES ⁺) 477 [MH ⁺]
82 (b)			32	¹ Hnmr (CDCl ₃ , 400MHz) δ: 0.20 (m, 2H), 0.57 (m, 2H), 0.72 (m, 2H), 1.00 (m, 2H), 2.60 (d, 2H), 3.32 (m, 1H), 3.85 (s, 3H), 4.03 (t, 2H), 4.13 (t, 2H), 4.91 (s, 2H), 6.37 (d, 1H), 6.65 (s, 1H), 6.77 (s, 1H). LRMS: m/z (ES ⁺) 392 [MH ⁺]
83 ^o (a)			80	¹ Hnmr (DMSOd ₆ , 400MHz) δ: 0.65 (m, 2H), 0.93 (m, 2H), 2.95 (m, 4H), 3.49 (m, 1H), 3.69 (m, 4H), 3.77 (s, 3H), 3.90 (t, 2H), 3.92 (t, 2H), 4.76 (s, 2H), 6.17 (d, 1H), 6.50 (s, 1H), 6.54 (d, 1H), 11.12 (s, 1H). LRMS: m/z (ES ⁺) 445 [MNa ⁺] Microanalysis found: C, 62.44; H, 6.21; N, 19.60. C ₂₂ H ₂₆ N ₆ O ₃ requires; C, 62.54; H, 6.20; N, 19.89%.

Ex No. (Method)	R1	R2	Yield %	Spectroscopic and analytical data
84 ^D (a)			66	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 0.66 (m, 2H), 0.93 (m, 2H), 1.59 (d, 1H), 1.80 (d, 1H), 2.45 (d, 1H), 2.76 (d, 1H), 2.94 (t, 2H), 3.47 (s, 1H), 3.52 (d, 2H), 3.77 (m, 5H), 3.01 (d, 1H), 3.95 (t, 2H), 4.33 (s, 1H), 4.78 (s, 2H), 6.14 (d, 1H), 6.53 (d, 1H), 7.29 (d, 1H), 7.56 (d, 1H), 11.09 (s, 1H). LRMS: m/z (ES ⁺) 482 [MNa ⁺] Microanalysis: Found: C, 67.67; H, 6.38; N, 15.12; C ₂₆ H ₂₉ N ₅ O ₃ requires; C, 67.96; H, 6.36; N, 15.24%
85 ^D (c)			70	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 1.30 (m, 5H), 1.79 (m, 5H), 2.38 (m, 4H), 2.94 (t, 2H), 3.52 (s, 2H), 3.57 (m, 4H), 3.79 (s, 3H), 3.93 (t, 2H), 4.14 (t, 1H), 4.77 (s, 2H), 6.57 (m, 2H), 7.27 (d, 1H), 7.57 (d, 1H), 11.03 (s, 1H). LRMS: m/z (APCI ⁺) 490 [MH ⁺]. Microanalysis: Found: C, 68.84; H, 7.33; N, 14.18; C ₂₈ H ₃₅ N ₅ O ₃ requires; C, 68.69; H, 7.21; N, 14.30% M.p. 233-235°C

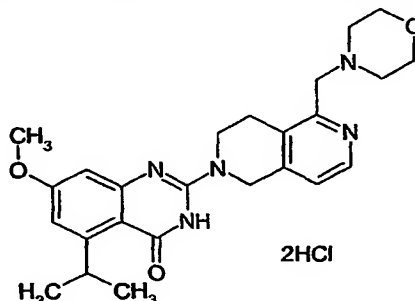
Ex No. (Method)	R1	R2	Yield %	Spectroscopic and analytical data
86 ^D (a)			76	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 1.16(d, 6H), 2.72 (t, 2H), 3.28 (s, 3H), 3.39 (m, 2H), 3.44 (m, 2H), 3.80 (s, 3H), 3.87 (t, 2H), 4.54 (m, 3H), 6.19 (s, 1H), 6.38 (d, 1H), 6.58 (2xs, 2H), 7.15 (d, 1H), 10.84 (s, 1H) LRMS: m/z (ES ⁺) 424 [MH ⁺] Microanalysis: Found: C, 65.18; H, 7.00; N, 16.41; C ₂₃ H ₂₉ N ₅ O ₃ requires; C, 65.23; H, 6.90; N, 16.54% M.p. 160-162°C

D = N,N-Diisopropylethylamine was used as the base

5 1 = N-(1,2,3,4-tetrahydro-5-isoquinolinyll)methanesulfonamide (WO 9830560) was used as the starting amine.

2 = N,N-diethyl-N-(1,2,3,4-tetrahydro-5-isoquinolinyllmethyl)amine (WO 9830560) was used as the starting amine

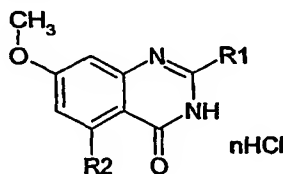
10 3 = 2-methyl-5,6,7,8-tetrahydro[1,6]naphthyridine (Chem. Pharm. Bull. 1984; 32 (7); 2522) was used as the starting amine

Example 875-Isopropyl-7-methoxy-2-(5-morpholin-4-ylmethyl-3,4-dihydro-1H-[2,6]naphthyridin-2-yl)-3H-quinazolin-4-one dihydrochloride

- 5 The chloro compound from preparation 269 (76 mg, 0.3 mmol) was mixed with the naphthyridine from preparation 117 (93 mg, 0.4 mmol) and N,N-diisopropylethylamine (129 μ l, 1 mmol) in n-butanol (5 ml) and the mixture was heated under reflux for 2 hours. The reaction mixture was cooled to room temperature and ethyl acetate added. The solution was washed with water and brine then dried over magnesium sulphate.
- 10 The residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 0:100 to 7:93). The material obtained was dissolved in dichloromethane and ethereal hydrogen chloride (1M, 2 ml) was added. The solvent was evaporated under reduced pressure to give the title compound as an off white solid (73 mg).
- 15 ¹H-NMR (DMSO-d₆, 400 MHz) δ : 1.14 (d, 6H), 2.96 (t, 2H), 3.35 (m, 4H), 3.82 (s, 3H), 3.91 (m, 4H), 4.00 (t, 2H), 4.51 (m, 1H), 4.55 (s, 2H), 4.95 (s, 2H), 6.68 (s, 1H), 6.91 (s, 1H), 7.33 (d, 1H), 8.47 (d, 1H)
- LRMS: m/z (ES⁺) 450 [MH⁺]
- Microanalysis: Found: C, 57.77; H, 6.65; N, 13.25. C₂₅H₃₁N₅O₃ 2HCl requires; C, 57.47; H, 6.37; N, 13.40%
- 20

Examples 88 to 122

The compounds of the following tabulated examples, (where n represents 1, 2 or 3 depending on the nature of R1), of the general formula:



were prepared by the general method outlined below using the appropriate chloro compound and the cyclic amine.

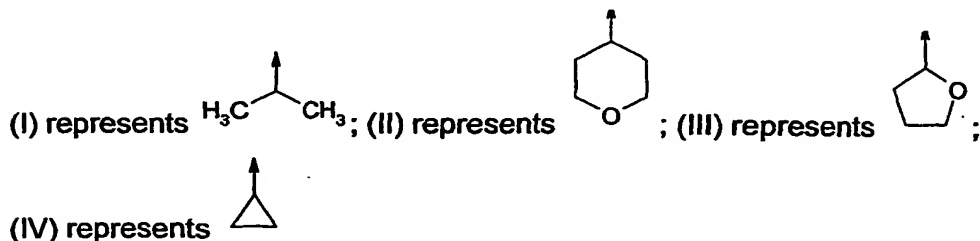
General Procedure for hydrochloride salts.

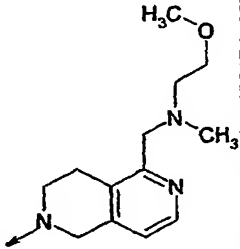
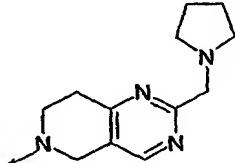
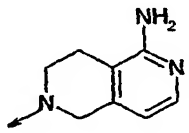
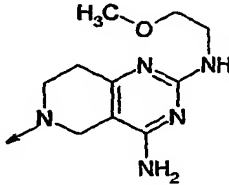
- 5 To a solution of the chloro-quinazolinone (1eq) in n-butanol (15ml per mmol) under nitrogen was added N,N-diisopropylethylamine or triethylamine (1.7-8eq) and the appropriate secondary amine (1-2eq). The resultant mixture was then heated under reflux for 1-6 hours, cooled and the product was isolated by filtration, washing with n-butanol and diethyl ether (method a)
- 10 Some reaction mixtures were concentrated under reduced pressure, the residue partitioned between dichloromethane and water, the organic phase separated, dried (MgSO_4) and evaporated under reduced pressure, (method b).
- Some products were additionally purified by column chromatography on silica gel using dichloromethane: methanol or dichloromethane: methanol: 0.88 ammonia as eluants,
- 15 (method c).

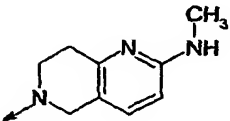
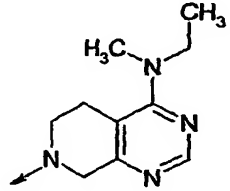
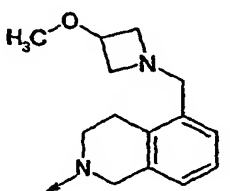
The products that were obtained were dissolved in dichloromethane and ethereal hydrogen chloride solution was added. The solvents were evaporated under reduced pressure to give the product as the hydrochloride salt.

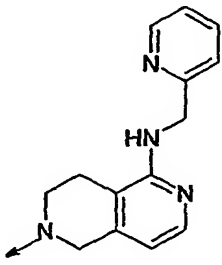
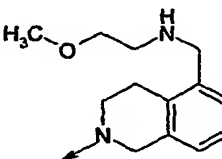
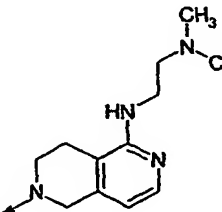
20

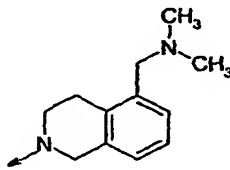
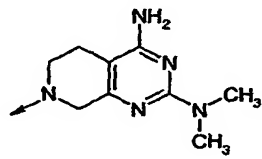
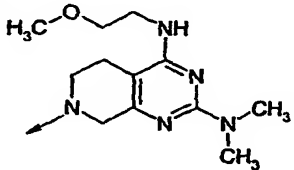
In the table following:

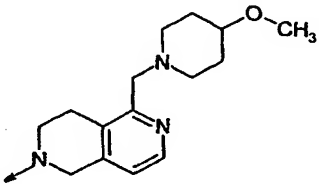
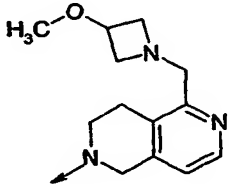


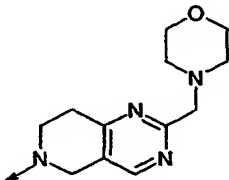
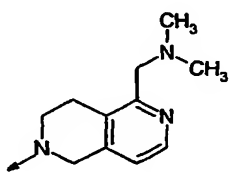
Ex No. (method)	R1	R2	Yield %	Spectroscopic and analytical data
88 (c)		(I)	55	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 1.17 (d, 6H), 2.87 (s, 3H), 2.96 (t, 2H), 3.26 (s, 3H), 3.40 (t, 2H), 3.73 (t, 2H), 3.82 (s, 3H), 4.09 (t, 2H), 4.42 (m, 1H), 4.54 (s, 2H), 5.07 (s, 2H), 6.78 (s, 1H), 7.29 (d, 1H), 7.41 (s, 1H), 8.43 (d, 1H). LRMS: m/z (ES ⁺) 452 [MH ⁺] Microanalysis: Found: C, 55.84; H, 6.85; N, 12.82. C ₂₅ H ₃₃ N ₅ O ₃ 2HCl 0.75H ₂ O requires; C, 55.81; H, 6.84; N, 13.02 %
89 (c)		(I)	41	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 1.25 (d, 6H), 1.88 (s, 4H), 2.85 (s, 4H), 3.14 (t, 2H), 3.88 (s, 3H), 4.06 (m, 4H), 4.57 (m, 1H), 4.91 (s, 2H), 6.72 (d, 1H), 6.76 (d, 1H), 6.55 (s, 1H). LRMS: m/z (ES ⁺) 435 [MH ⁺]
90 ^D (a)		(I)	91	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 1.16 (d, 6H), 2.66 (t, 2H), 3.80 (s, 3H), 3.98 (t, 2H), 4.50 (m, 1H), 4.88 (s, 2H), 6.70 (s, 1H), 6.77 (d, 1H), 6.88 (s, 1H), 7.83 (d, 1H), 7.93 (s, 2H). LRMS: m/z (ES ⁺) 444 [MH ⁺]
91 (a)		(I)	77	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 1.18 (d, 6H), 2.82 (m, 2H), 3.27 (s, 3H), 3.46 (m, 2H), 3.51 (m, 2H), 3.80 (s, 3H), 4.00 (t, 2H), 4.48 (m, 1H), 4.60 (s, 2H), 6.79 (s, 1H), 7.30 (s, 1H), 7.68 (s, 2H), 8.45 (s, 1H). LRMS: m/z (ES ⁺) 440 [MH ⁺]. Microanalysis: Found: C, 51.50; H, 6.13; N, 18.97; C ₂₂ H ₂₉ N ₇ O ₃ 2 HCl requires: C, 51.57; H, 6.10; N, 19.13%

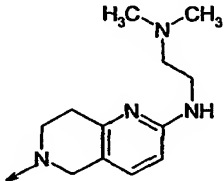
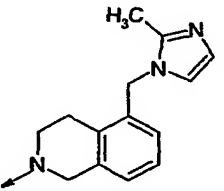
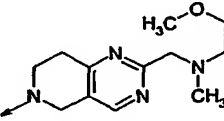
Ex No. (method)	R1	R2	Yield %	Spectroscopic and analytical data
92 (a)		(I)	78	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 1.19 (d, 6H), 3.00 (s, 3H), 3.13 (m, 2H), 3.82 (s, 3H), 4.07 (m, 2H), 4.42 (m, 1H), 4.83 (s, 2H), 6.80 (d, 1H), 6.98 (d, 1H), 7.37 (s, 1H), 7.69 (d, 1H). LRMS: m/z (ES ⁺) 480 [MH ⁺]
93 (a)		(I)	73	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 1.19 (m, 9H), 3.00 (m, 2H), 3.28 (s, 3H), 3.70 (q, 2H), 3.84 (s, 3H), 3.94 (m, 2H), 4.48 (m, 1H), 4.95 (s, 2H), 6.75 (s, 1H), 7.08 (s, 1H), 8.60 (s, 1H). LRMS: m/z (ES ⁺) 409 [MH ⁺]. Microanalysis: Found: C, 54.90; H, 6.49; N, 17.41 C ₂₂ H ₂₈ N ₆ O ₂ 2HCl requires; C, 54.89; H, 6.28; N, 17.46%
94 (a)		(I)	35	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 1.17 (d, 6H), 3.03 (m, 2H), 3.25 (s, 2H), 3.40 (s, 2H), 3.82 (m, 4H), 3.97 (m, 4H), 4.26 (m, 3H), 4.43 (s, 1H), 4.52 (m, 1H), 4.90 (s, 2H), 6.90 (s, 1H), 7.30 (m, 3H). LRMS: m/z (ES ⁺) 449 [MH ⁺]. Microanalysis: Found: C, 58.97; H, 6.63; N, 10.60 C ₂₆ H ₃₂ N ₄ O ₃ 2HCl 0.4 H ₂ O requires; C, 59.07; H, 6.63; N, 10.60%

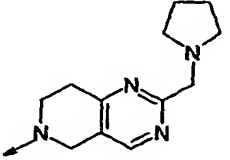
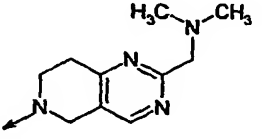
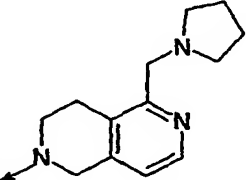
Ex No. (method)	R1	R2	Yield %	Spectroscopic and analytical data
95 (c)		(I)	61	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 1.17 (d, 6H), 2.82 (m, 2H), 3.82 (s, 3H), 4.13 (m, 2H), 4.44 (m, 1H), 5.00 (s, 4H), 6.75 (d, 1H), 6.79 (s, 1H), 7.32 (s, 1H), 7.54 (m, 1H), 7.68 (d, 1H), 7.78 (d, 1H), 8.07 (m, 1H), 8.63 (d, 1H). LRMS: m/z (ES ⁺) 457 [MH ⁺]. Microanalysis: Found: C, 54.01; H, 5.75; N, 14.06; C ₂₆ H ₂₈ N ₆ O ₂ 3HCl 0.6 H ₂ O requires; C, 54.15; H, 5.63; N, 14.57%
96 (c)		(I)	56	¹ H-NMR (CDCl ₃ , 400 MHz) δ: 1.23 (d, 6H), 2.82 (t, 2H), 3.06 (t, 2H), 3.34 (s, 3H), 3.50 (t, 2H), 3.80 (s, 3H), 3.86 (m, 4H), 4.76 (m, 1H), 4.80 (s, 2H), 6.70 (s, 2H), 7.10 (m, 1H), 7.20 (m, 2H). LRMS: m/z (ES ⁺) 437 [MH ⁺]. Microanalysis: Found: C, 55.36; H, 6.78; N, 10.14. C ₂₅ H ₃₂ N ₄ O ₃ 2HCl 0.5 CH ₂ Cl ₂ requires; C, 55.49; H, 6.39; N, 10.15 %
97 (c)		(I)	65	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 1.16 (d, 6H), 2.82 (s, 6H), 2.89 (m, 2H), 3.38 (t, 2H), 3.84 (s, 3H), 4.04 (m, 2H), 4.09 (m, 2H), 4.43 (m, 1H), 4.90 (s, 1H), 5.02 (s, 2H), 6.78 (m, 2H), 7.30 (s, 1H), 7.80 (d, 1H), 8.41 (s, 1H), 10.80 (s, 1H). LRMS: m/z (ES ⁺) 437 [MH ⁺]. Microanalysis: Found: C, 52.19; H, 6.79; N, 14.92; C ₂₄ H ₃₂ N ₆ O ₃ 3HCl 0.5H ₂ O requires; C, 51.94; H, 6.54; N, 15.14 %

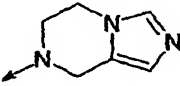
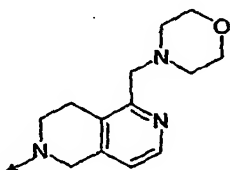
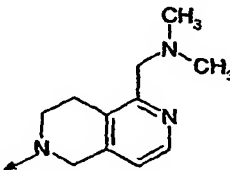
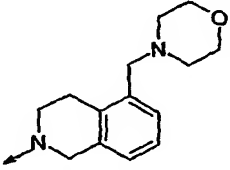
Ex No. (method)	R1	R2	Yield %	Spectroscopic and analytical data
98 (c)		(I)	40	¹ H-NMR (CDCl ₃ , 400 MHz) δ: 1.24 (d, 6H), 2.20 (s, 6H), 3.09 (t, 2H), 3.38 (s, 2H), 3.85 (m, 5H), 4.56 (m, 1H), 4.80 (s, 2H), 6.70 (s, 2H), 7.15 (m, 3H). LRMS: m/z (ES ⁺) 407 [MH ⁺]
99 (a)		A	66	¹ H-NMR (DMSOd ₆ , 400 MHz) δ: 1.17 (d, 6H), 2.53 (m, 2H), 3.17 (s, 6H), 3.81 (s, 3H), 4.00 (m, 2H), 4.48 (m, 1H), 4.85 (s, 2H), 6.78 (s, 1H), 7.12 (s, 1H). LRMS: m/z (ES ⁺) 410 [MH ⁺]. Microanalysis: Found: C, 50.81; H, 6.16; N, 19.44; C ₂₁ H ₂₇ N ₇ O ₂ · 2HCl · 0.75 H ₂ O requires; C, 50.86; H, 6.20; N, 19.77%
100 (a)		(I)	99	¹ H-NMR (DMSOd ₆ , 400 MHz) δ: 1.16 (d, 6H), 3.16 (s, 6H), 3.24 (s, 3H), 3.50 (t, 2H), 3.59 (t, 3H), 3.80 (s, 3H), 3.90 (m, 2H), 4.50 (m, 1H), 4.73 (s, 2H), 6.72 (s, 1H), 6.80 (s, 1H), 8.38 (t, 1H). LRMS: m/z (ES ⁺) 468 [MH ⁺]. Microanalysis: Found: C, 53.27; H, 6.66; N, 17.99 C ₂₄ H ₃₃ N ₇ O ₃ · 2HCl requires; C, 53.33; H, 6.53; N, 18.14%

Ex No. (method)	R1	R2	Yield %	Spectroscopic and analytical data
101 ^D (a)		(I)	55	¹ H-nmr (CD ₃ OD, 400MHz) δ: 1.23 (d, 6H), 2.04 (m, 2H), 2.13 (m, 2H), 3.03 (m, 2H), 3.39 (m, 5H), 3.50 (m, 2H), 3.62 (m, 1H), 3.93 (s, 3H), 4.07 (m, 2H), 4.49 (m, 1H), 4.55 (s, 2H), 4.98 (s, 2H), 6.91 (s, 1H), 6.99 (s, 1H), 7.35 (d, 1H), 8.53 (d, 1H). LRMS: m/z (ES ⁺) 478 [MH ⁺]. Microanalysis found: C, 58.97; H, 6.92; N, 12.71; C ₂₇ H ₃₅ N ₅ O ₃ 2 HCl requires C, 58.91; H, 6.77; N, 12.72%.
102 (c)		(I)	45	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 1.18 (d, 6H), 1.26 (m, 2H), 2.91 (m, 2H), 3.25 (s, 3H), 3.82 (s, 3H), 4.08 (m, 4H), 4.32 (m, 1H), 4.41 (m, 1H), 4.64 (s, 2H), 5.04 (s, 2H), 6.78 (s, 1H), 7.23 (d, 1H), 7.10 (s, 1H), 8.38 (d, 1H), 10.78 (s, 1H). LRMS: m/z (ES ⁺) 450 [MH ⁺]. Microanalysis found: C, 55.62; H, 6.41; 12.78; C ₂₅ H ₃₁ N ₅ O ₃ 2HCl H ₂ O requires; C, 55.56; H, 6.53; 12.96%.

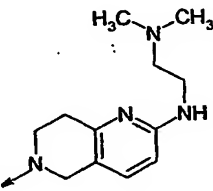
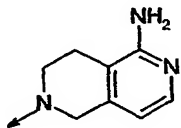
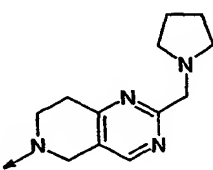
Ex No. (method)	R1	R2	Yield %	Spectroscopic and analytical data
103 (b)		(I)	63	¹ H-NMR (CDCl ₃ , 400 MHz) δ: 1.25 (d, 6H), 2.59 (m, 4H), 3.14 (t, 2H), 3.76 (m, 6H), 3.88 (s, 3H), 4.00 (t, 2H), 4.54 (m, 1H), 4.89 (s, 2H), 6.71 (d, 1H), 6.76 (d, 1H), 8.57 (s, 1H), 9.75 (s, 1H). LRMS: m/z (ES ⁺) 473 [MH ⁺] Microanalysis: Found: C, 54.49; H, 6.41; N, 15.58. C ₂₄ H ₃₀ N ₆ O ₃ 2 HCl 0.25 H ₂ O requires; C, 54.60; H, 6.20; N, 15.92 %
104 (c)		(I)	40	¹ H NMR (DMSOd ₆ , 400MHz) δ: 1.18 (d, 6H), 2.87 (s, 6H), 2.95 (t, 2H), 3.83 (s, 3H), 4.08 (t, 2H), 4.46 (m, 1H), 4.52 (s, 2H), 5.04 (s, 2H), 6.72 (s, 1H), 7.31 (m, 2H), 8.46 (d, 1H). LRMS: m/z (ES ⁺) 408 [MH ⁺] Microanalysis: Found: C, 54.47; H, 6.62; N, 13.65. C ₂₃ H ₂₉ N ₅ O ₂ 2HCl 1.5H ₂ O requires C, 54.44; H, 6.75; N, 13.80 %

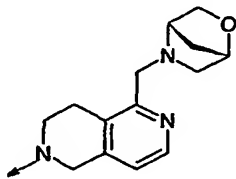
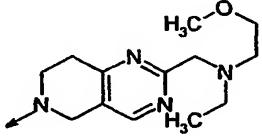
Ex No. (method)	R1	R2	Yield %	Spectroscopic and analytical data
105 (c)		(I)	61	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 1.08 (d, 6H), 2.80 (s, 6H), 3.18 (s, 2H), 3.33 (t, 2H), 3.82 (s, 3H), 3.95 (m, 2H), 4.09 (m, 2H), 4.42 (m, 1H), 4.07 (s, 2H), 6.80 (s, 1H), 7.04 (d, 1H), 7.42 (s, 1H), 7.70 (d, 1H). LRMS: m/z (ES ⁺) 437 [MH ⁺] Microanalysis: Found: C, 51.75; H, 6.72; N, 14.93. C ₂₄ H ₃₂ N ₆ O ₃ 3HCl 0.6 H ₂ O requires C, 51.78; H, 6.53; N, 15.09 %
106 (c)		(I)	88	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 1.20 (d, 6H), 2.60 (s, 3H), 2.96 (t, 2H), 3.86 (s, 3H), 4.08 (t, 2H), 4.42 (m, 1H), 5.05 (s, 2H), 5.42 (s, 2H), 6.80 (s, 1H), 6.84 (d, 1H), 7.26 (m, 2H), 7.41 (s, 1H), 7.58 (s, 2H). LRMS: m/z (ES ⁺) 444 [MH ⁺]. Microanalysis: Found: C, 59.19; H, 6.47; N, 13.28; C ₂₆ H ₂₉ N ₅ O ₂ 2HCl 0.6H ₂ O requires; C, 59.23; H, 6.16; 13.28%
107 (c)		(II)	67	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 1.64 (m, 4H), 2.48 (s, 2H), 2.90 (s, 3H), 3.07 (t, 3H), 3.26 (s, 3H), 3.42 (t, 2H), 3.70 (t, 2H), 3.80 (s, 3H), 3.93 (m, 2H), 4.05 (t, 2H), 4.32 (m, 1H), 4.58 (s, 2H), 4.92 (s, 2H), 6.86 (s, 1H), 6.93 (s, 1H), 8.74 (s, 1H), 10.17 (s, 1H). LRMS: m/z (ES ⁺) 495 [MH ⁺]. Microanalysis found: C, 55.21; H, 6.59; N, 14.71; C ₂₆ H ₃₄ N ₆ O ₄ 2HCl requires; C, 55.03; H, 6.39; N, 14.81%

Ex No. (method)	R1	R2	Yield %	Spectroscopic and analytical data
108 (a)		(II)	57	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 1.64 (m, 4H), 1.98 (m, 4H), 3.12 (m, 4H), 3.42 (m, 2H), 3.61 (s, 2H), 3.81 (s, 3H), 3.97 (m, 2H), 4.18 (s, 2H), 4.22 (m, 1H), 4.62 (m, 2H), 5.08 (s, 2H), 6.78 (s, 1H), 7.39 (s, 1H), 8.76 (s, 1H), 10.73 (s, 1H) LRMS: m/z (ES ⁺) 477 [MH ⁺]
109 (c)		(II)	71	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 1.62 (m, 4H), 2.86 (s, 6H), 3.09 (t, 3H), 3.42 (m, 2H), 3.81 (s, 3H), 3.93 (m, 2H), 4.11 (m, 2H), 4.27 (m, 1H), 4.57 (s, 2H), 5.06 (s, 2H), 6.77 (s, 1H), 8.76 (s, 1H), 10.37 (s, 1H). LRMS: m/z (ES ⁺) 449 [MH ⁺] Microanalysis found: C, 56.66; H, 6.47; N, 16.33; C ₂₄ H ₃₀ N ₆ O ₃ 1.6 HCl requires; C, 56.65; H, 6.26; N, 16.51%
110 (c)		(II)	60	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 1.64 (m, 4H), 1.98 (m, 4H), 2.95 (m, 2H), 3.40 (m, 6H), 3.80 (s, 3H), 3.99 (m, 4H), 4.32 (m, 1H), 4.59 (s, 2H), 4.95 (s, 2H), 6.63 (s, 1H), 7.30 (d, 1H), 8.42 (d, 1H), 10.27 (s, 1H). LRMS: m/z (ES ⁺) 467 [MH ⁺]

Ex No. (method)	R1	R2	Yield %	Spectroscopic and analytical data
111 (a)		(II)	75	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 1.66 (m, 4H), 2.46 (s, 2H), 3.42 (t, 2H), 3.81 (s, 3H), 3.93 (d, 2H), 4.23 (m, 3H), 4.43 (s, 2H), 5.08 (s, 2H), 6.74 (s, 1H), 7.22 (s, 1H), 7.61 (s, 1H), 9.15 (s, 1H). LRMS: m/z (ES ⁺) 482 [MH ⁺]. Microanalysis found: C, 54.95; H, 5.86; N, 15.77; C ₂₀ H ₂₃ N ₅ O ₃ HCl H ₂ O requires; C, 55.11; H, 6.01; N, 16.07%
112 (c)		(II)	18	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 1.66 (m, 4H), 3.03 (m, 2H), 3.35 (s, 4H), 3.43 (m, 2H), 3.84 (s, 3H), 3.90 (s, 6H), 4.13 (s, 2H), 4.24 (m, 1H), 4.57 (s, 2H), 5.13 (s, 2H), 6.78 (s, 1H), 7.32 (d, 1H), 7.58 (s, 1H), 8.47 (d, 1H), 11.0 (s, 1H). LRMS: m/z (ES ⁺) 492 [MH ⁺]
113 (c)		(II)	10	¹ H-nmr (CD ₃ OD, 400MHz) δ: 1.67 (m, 4H), 2.87 (s, 6H), 3.15 (s, 2H), 3.43 (m, 2H), 3.81 (s, 3H), 3.95 (m, 2H), 4.00 (s, 2H), 4.32 (m, 1H), 4.54 (s, 2H), 4.98 (s, 2H), 6.69 (s, 1H), 7.30 (d, 1H), 8.46 (d, 1H). LRMS: m/z (ES ⁺) 450 [MH ⁺]
114 (c)		(II)	77	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 1.63 (m, 4H), 3.15 (s, 4H), 3.22 (t, 2H), 3.42 (m, 3H), 3.88 (m, 11H), 4.28 (m, 1H), 4.38 (s, 2H), 4.92 (s, 2H), 6.73 (s, 1H), 7.27 (s, 1H), 7.33 (d, 1H), 7.61 (d, 1H), 11.17 (s, 1H). LRMS: m/z (ES ⁺) 491 [MH ⁺]; Microanalysis found: C, 58.45; H, 6.54; N, 9.58; C ₂₈ H ₃₄ N ₄ O ₄ 2HCl 0.65 H ₂ O requires; C, 58.46; H, 6.54; N, 9.74%

Ex No. (method)	R1	R2	Yield %	Spectroscopic and analytical data
115 (a)		(II)	70	¹ H NMR (DMSO-d ₆ , 400MHz) δ: 1.67 (m, 4H), 3.12 (s, 2H), 3.22 (s, 3H), 3.42 (m, 2H), 3.82 (s, 3H), 3.94 (m, 12H), 5.01 (s, 2H), 6.79 (s, 1H), 7.32 (m, 2H), 7.51 (m, 2H), 11.47 (s, 1H). LRMS: m/z (ES ⁺) 491 [MH ⁺]. Microanalysis found: C, 58.76; H, 6.53; N, 9.65; C ₂₈ H ₃₄ N ₄ O ₄ 2HCl 0.5 H ₂ O requires; C, 58.74; H, 6.51; N, 9.79%
116 (c)		(III)	83	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 1.47 (m, 1H), 1.90 (m, 6H), 2.52 (m, 2H), 3.35 (m, 6H), 3.90 (m, 11H), 4.80 (s, 2H), 5.80 (t, 1H), 6.98 (s, 1H), 7.00 (d, 1H), 7.19 (s, 1H), 7.71 (d, 1H). LRMS: m/z (ES ⁺) 491 [MH ⁺]. Microanalysis: Found: C, 53.69; H, 6.54; N, 13.89; C ₂₇ H ₃₄ N ₆ O ₃ 3HCl 0.25H ₂ O requires; C, 53.65; H, 6.25; N, 13.90%
117 (a)		(III)	54	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 1.49 (m, 1H), 1.82 (m, 2H), 2.50 (m, 2H), 3.08 (m, 2H), 3.28 (s, 3H), 3.53 (t, 2H), 3.61 (m, 2H), 3.80 (m, 4H), 4.02 (m, 3H), 4.78 (s, 2H), 5.80 (t, 1H), 6.94 (d, 1H), 7.02 (d, 1H), 7.12 (s, 1H), 7.72 (d, 1H). LRMS: m/z (ES ⁺) 452 [MH ⁺]. Microanalysis: Found: C, 53.37; H, 5.97; N, 12.66; C ₂₄ H ₂₉ N ₅ O ₄ 2HCl 0.25 CH ₂ Cl ₂ requires; C, 53.38; H, 5.82, 12.83%

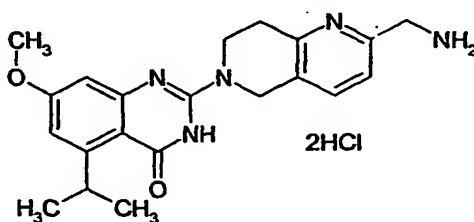
Ex No. (method)	R1	R2	Yield %	Spectroscopic and analytical data
118 (c)		(III)	87	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 1.50 (m, 1H), 1.82 (m, 2H), 2.51 (m, 2H), 2.81 (s, 6H), 3.11 (m, 2H), 3.32 (t, 2H), 3.82 (m, 4H), 3.91 (m, 2H), 4.01 (m, 3H), 4.80 (s, 2H), 5.80 (t, 1H), 6.95 (s, 1H), 6.99 (d, 1H), 7.13 (s, 1H), 7.69 (d, 1H). LRMS: m/z (ES ⁺) 465 [MH ⁺]. Microanalysis: Found: C, 52.32; H, 6.45; N, 14.66; C ₂₅ H ₃₂ N ₆ O ₃ 3HCl requires; C, 52.32; H, 6.15; N, 14.64%
119 (a)		(III)	89	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 1.49 (m, 1H), 1.80 (m, 2H), 2.50 (m, 2H), 3.80 (m, 5H), 4.06 (m, 3H), 4.98 (s, 2H), 5.79 (m, 1H), 6.73 (d, 1H), 7.95 (d, 1H), 7.22 (s, 1H), 7.86 (d, 1H), 8.08 (s, 2H). LRMS: m/z (ES ⁺) 394 [MH ⁺]. Microanalysis: Found: C, 50.46; H, 5.22; N, 13.68; C ₂₁ H ₂₃ N ₅ O ₃ 3HCl requires; C, 50.16; H, 5.21; N, 13.93%
120 (a)		-Cl	17	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 1.64 (s, 4H), 2.51 (s, 4H), 2.93 (m, 2H), 3.73 (s, 2H), 3.81 (s, 3H), 3.95 (t, 2H), 4.81 (s, 2H), 6.70 (s, 1H), 6.73 (s, 1H), 8.58 (s, 1H). LRMS: m/z (ES ⁺) 427, 427 [MH ⁺] M.p. 190-191°C

Ex No. (method)	R1	R2	Yield %	Spectroscopic and analytical data
121 (a)		-Cl	45	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 2.02 (d, 1H), 2.40 (d, 1H), 2.90 (s, 2H), 3.42 (m, 1H), 3.74 (d, 1H), 3.82 (s, 3H), 4.02 (m, 2H), 4.28 (d, 1H), 4.48 (s, 1H), 4.65 (m, 4H), 4.97 (s, 2H), 6.81 (s, 1H), 7.00 (s, 1H), 7.30 (d, 1H), 8.42 (d, 1H). LRMS: m/z (ES ⁺) 454, 456 [MH ⁺]. M.p. 314-315°C
122 (c)		(IV)		¹ H-nmr (CDCl ₃ + TFAAd, 400MHz) δ: 0.77 (m, 2H), 1.14 (m, 2H), 1.44 (t, 3H), 2.96 (m, 1H), 3.36 (t, 2H), 3.39 (s, 3H), 3.54 (q, 2H), 3.60 (m, 2H), 3.80 (m, 2H), 3.88 (s, 3H), 4.18 (m, 2H), 4.66 (m, 1H), 4.80 (m, 1H), 5.16 (s, 2H), 6.62 (s, 1H), 6.99 (s, 1H), 8.70 (s, 1H). LRMS: m/z (ES ⁺) 487 [MNa ⁺]. Microanalysis found: C, 59.08; H, 6.85; N, 16.08. C ₂₅ H ₃₂ N ₆ O ₃ ·HCl; 0.5H ₂ O requires C, 58.87; H, 6.72; N, 16.48%.

D Triethylamine was used as the base

Example 123

2-(2-Aminomethyl-7,8-dihydro-5H-[1,6]naphthyridin-6-yl)-5-isopropyl-7-methoxy-3H-quinazolin-4-one dihydrochloride



Hydrogen chloride gas was bubbled for 10 minutes into a solution of the protected amine from preparation 293 (155 mg, 0.32 mmol) in dichloromethane at 0°C. The solution was stirred at 0°C for 1.5 hours and then the mixture was degassed by a

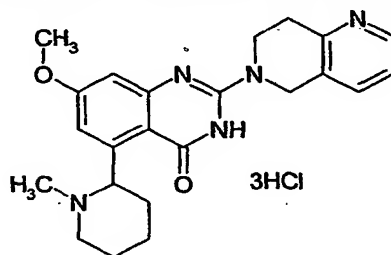
stream of nitrogen being blown through the mixture. The solvent was evaporated under reduced pressure and the residue was dried under vacuum to give the title compound as a white solid (146 mg).

¹H-nmr (CD₃OD, 400MHz) δ: 1.23 (d, 6H), 3.21 (t, 2H), 3.90 (s, 3H), 4.07 (t, 2H), 4.06 (s, 2H), 4.48 (m, 1H), 4.94 (s, 2H), 6.86 (s, 1H), 6.90 (s, 1H), 7.33 (d, 1H), 7.72 (d, 1H)
LRMS: m/z (ES⁺) 380 [MH⁺]

Microanalysis: Found: C, 55.61; H, 6.21; N, 15.12; C₂₁H₂₅N₅O₂ 2HCl requires; C, 55.76; H, 6.02; N, 15.48%

Example 124

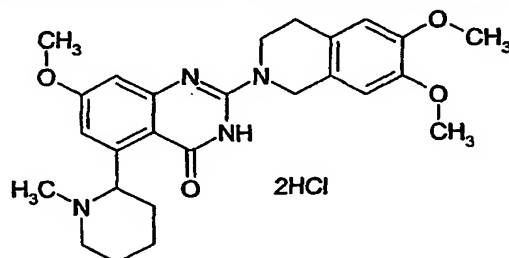
2-(7,8-Dihydro-5H-[1,6]naphththyridin-6-yl)-7-methoxy-5-(1-methyl-piperidin-2-yl)-3H-quinazolin-4-one trihydrochloride



3-Methylpentan-3-ol (5 ml) was added to the guanidine from preparation 286 (86 mg, 0.2 mmol) and potassium *t*-butoxide (67 mg, 0.6 mmol) and the mixture was heated under reflux for 1 hour. A further quantity of potassium *t*-butoxide (45 mg, 0.4 mmol) was added and the mixture was heated under reflux for a further 1 hour. The reaction mixture was cooled to room temperature and 1M citric acid (3 ml) was added. The mixture was added to water and was basified with 0.5M sodium hydroxide solution. The solution was extracted with dichloromethane (3x50 ml) and the combined organic solutions were dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol and ammonium hydroxide in dichloromethane as eluant (gradient from 0:0:100 to 10:1:90). The material isolated was dissolved in dichloromethane and 1M hydrogen chloride in dichloromethane was added. The mixture was evaporated under reduced pressure to give the title compound as a white solid (26 mg).

¹H-nmr (DMSO-d₆ 400MHz) δ: 1.80 (m, 10H), 2.40 (m, 2H), 3.08 (m, 1H), 3.49 (m, 2H), 3.97 (s, 3H), 4.12 (m, 2H), 5.07 (s, 2H), 7.77 (m, 1H), 8.00 (d, 1H), 8.60 (m, 1H), 8.63 (d, 1H)

LRMS: m/z (ES⁺) 406 [MH⁺]

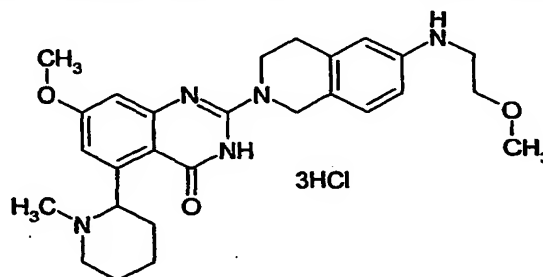
Example 1252-(6,7-Dimethoxy-3,4-dihydro-1H-isouquinolin-2-yl)-7-methoxy-5-(1-methyl-piperidin-2-yl)-3H-quinazolin-4-one dihydrochloride

- 5 The title compound was obtained from the guanidine from preparation 287 in 27% yield following the procedure described in Example 124.

¹H-nmr (DMSO-d₆ 400MHz) δ: 1.80 (m, 10H), 2.85 (t, 2H), 3.80 (m, 13H), 4.80 (s, 2H), 6.78 (d, 2H), 6.89 (d, 1H), 7.20 (s, 1H)

LRMS: m/z (ES⁺) 465 [MH⁺]

10

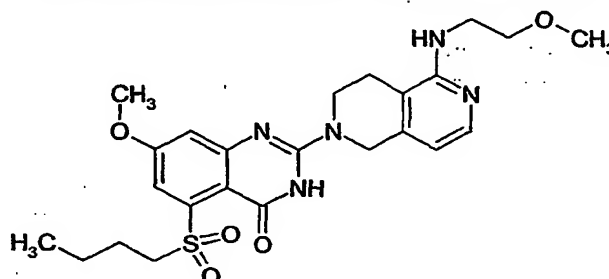
Example 1267-Methoxy-2-[2-(2-methoxy-ethylamino)-3,4-dihydro-1H-isouquinolin-2-yl]-5-(1-methyl-piperidin-2-yl)-3H-quinazolin-4-one trihydrochloride

- 15 The title compound was obtained from the guanidine from preparation 288 in 27% yield following a similar procedure to that described in Example 124.

¹H-nmr (DMSO-d₆ 400MHz) δ: 1.60 (m, 11H), 3.50 (m, 16H), 4.72 (s, 2H), 6.89 (d, 1H), 7.00 (d, 1H), 7.70 (m, 2H)

LRMS: m/z (ES⁺) 479 [MH⁺]

- 20 Microanalysis: Found: C, 53.53; H, 6.73; N, 13.66; C₂₆H₃₄N₆O₃ 3HCl 0.25 (CH₃CH₃)₂O requires; C, 53.47; H, 6.56; N, 13.86%

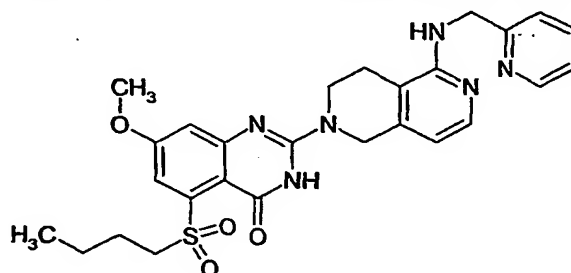
Example 1275-(Butane-1-sulfonyl)-7-methoxy-2-[5-(2-methoxy-ethylamino)-3,4-dihydro-1H-[2,6]naphthyridin-2-yl]-3H-quinazolin-4-one

5 Caesium carbonate (450 mg, 1.38 mmol) was added to the guanidine from preparation 224 (177 mg, 0.55 mmol) in N,N-dimethylformamide (2 ml) and the suspension was stirred for 1 hour at room temperature. The imidazolidine solution from preparation 280 (3 ml, 0.46 mmol) was added and the mixture was stirred at room temperature for 42 hours. The solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate (25 ml) and pH7 buffer (40 ml). The phases were separated and the aqueous solution was extracted with ethyl acetate (2x 25 ml). The combined organic solutions were washed with brine (3x15 ml), dried over magnesium sulphate and evaporated under reduced pressure.

15 The material obtained was dissolved in 1,2-dimethoxyethane (3 ml) and was added to potassium *tert*-butoxide (139 mg, 1.24 mmol) under a nitrogen atmosphere. The mixture was heated under reflux for 1.5 hours and then was cooled to room temperature and partitioned between dichloromethane (25 ml) and pH7 buffer. The phases were separated and the aqueous solution was extracted with dichloromethane (2x 25 ml). The combined organic solutions were dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 2:98 to 4:96). The material obtained was dried under vacuum at 60°C for 24 hours to give the title compound (29 mg).

25 ¹H-nmr (CDCl₃, 400MHz) δ: 0.89 (t, 3H), 1.42 (m, 2H), 1.72 (m, 2H), 2.63 (m, 2H), 3.38 (s, 3H), 3.59 (t, 2H), 3.68 (m, 2H), 3.79 (m, 2H), 3.93 (s, 3H), 3.98 (t, 2H), 4.55 (s, 1H), 4.72 (s, 2H), 6.44 (d, 1H), 7.00 (d, 1H), 7.72 (s, 1H), 7.99 (d, 1H)

LRMS: *m/z* ES⁺ 502 [MH⁺]

Example 1285-(Butane-1-sulfonyl)-7-methoxy-2-[5-[(pyridin-2-ylmethyl)-amino]-3,4-dihydro-1H-[2,6]naphthyridin-2-yl]-3H-quinazolin-4-one

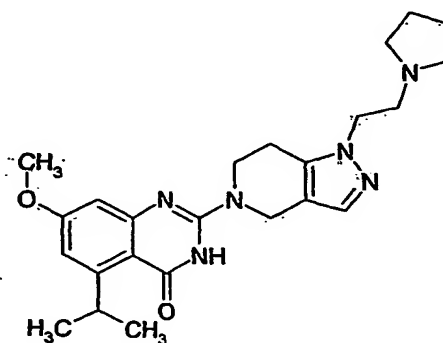
- 5 The title compound was obtained from the imidazolidine solution from preparation 280 and the guanidine from preparation 223 in 7% yield following the procedure described in Example 127.

¹H-nmr (CDCl₃, 400MHz) δ: 0.88 (t, 3H), 1.40 (m, 2H), 1.74 (m, 2H), 2.77 (t, 2H), 3.80 (m, 2H), 3.93 (s, 3H), 3.99 (t, 2H), 4.71 (s, 2H), 4.77 (d, 2H), 5.70 (m, 1H), 6.47 (d, 1H),
 10 7.00 (m, 1H), 7.16 (m, 1H), 7.29 (m, 1H), 7.64 (m, 1H), 7.72 (s, 1H), 8.01 (d, 1H), 8.56 (d, 1H)

LRMS: m/z (ES⁺) 535 [MH⁺]

Example 129

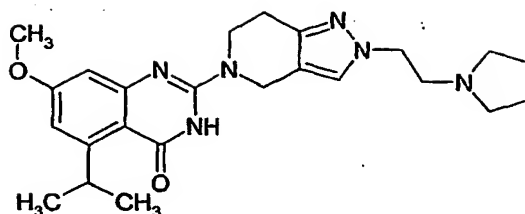
- 15 5-Isopropyl-7-methoxy-2-[1-(2-pyrrolidin-1-yl-ethyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-3H-quinazolin-4-one



and

Example 130

- 20 5-Isopropyl-7-methoxy-2-[2-(2-pyrrolidin-1-yl-ethyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-3H-quinazolin-4-one



The chloro compound from preparation 269 (91 mg, 0.36 mmol) was added to a mixture of the amines from preparation 229-A and preparation 229-B (60:40 mixture, 206 mg, 0.45 mmol) in *n*-butanol (3 ml) containing *N,N*-diisopropylethylamine (350 μ l, 2 mmol). The reaction mixture was heated under reflux for 2 hours and then was cooled to room temperature and diluted with ethyl acetate (350 ml). The organic mixture was washed with sodium hydrogen carbonate solution (2x15 ml), dried over magnesium sulphate and evaporated under reduced pressure.

The residue was purified by chromatography on a Chiralpak® AS 250mmx20 mm column, using diethylamine and propan-2ol in *n*-hexane (0.05:9.95:90) as eluant at a flow rate of 10 ml/minute to give the title compound of Example 129 (31 mg).

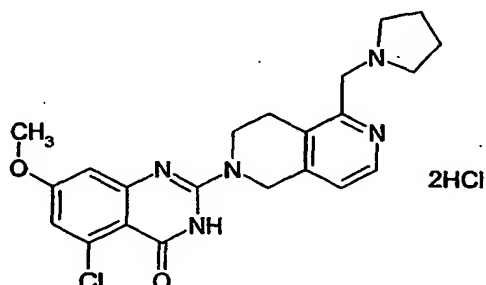
^1H -nmr (CD_3OD , 400MHz) δ : 1.20 (d, 6H), 1.72 (m, 4H), 2.52 (m, 4H), 2.90 (m, 4H), 3.84 (s, 3H), 3.99 (m, 2H), 4.16 (t, 2H), 2.53 (m, 1H), 4.65 (s, 2H), 6.71 (m, 2H), 7.35 (s, 1H)

LRMS: m/z (ES^+) 437 [MH^+]

Also isolated was the title compound of Example 130 (16 mg):

^1H -NMR: (CDCl_3 , 400 MHz) δ : 1.25 (d, 6H), 1.80 (m, 4H), 2.63 (m, 4H), 2.90 (m, 2H), 3.02 (m, 2H), 3.86 (s, 3H), 4.02 (m, 2H), 4.25 (m, 2H), 4.59 (m, 1H), 4.75 (s, 2H), 6.68 (s, 1H), 6.71 (s, 1H), 7.29 (s, 1H)

LRMS: m/z (ES^-) 435 [M-H]

Example 1315-Chloro-7-methoxy-2-(5-pyrrolidin-1-ylmethyl-3,4-dihydro-1H-[2,6]naphthyridin-2-yl)-3H-quinazolin-4-one dihydrochloride

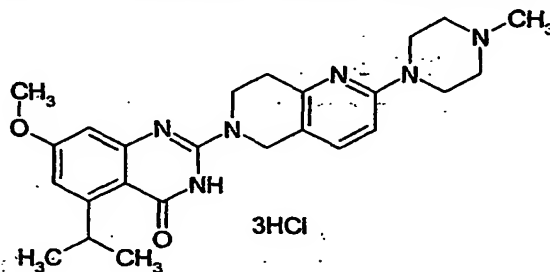
- 5 The title compound was obtained from the chloro compound from preparation 273 and the amine from preparation 113 in 74% yield following the procedure described in Example 86.

¹H-nmr (DMSO-d₆ 400MHz) δ: 1.63 (m, 4H), 2.41 (m, 4H), 3.00 (t, 2H), 4.69 (s, 2H), 3.80 (s, 3H), 3.88 (t, 2H), 4.81 (s, 2H), 6.68 (d, 1H), 6.71 (d, 1H), 7.12 (d, 1H), 8.24 (d, 1H), 11.20 (s, 1H)

LRMS: m/z (ES⁺) 426 [MH⁺]

Microanalysis: Found: C, 49.42; H, 5.63; N, 12.51; C₂₂H₂₄ClN₅O₂ 2HCl 2H₂O requires; C, 49.40; H, 5.65; N, 13.09%

15

Example 1325-Isopropyl-7-methoxy-2-[2-(4-methyl-piperazin-1-yl)-7,8-dihydro-5H-[1,6]naphthyridin-6-yl]-3H-quinazolin-4-one trihydrochloride

- 20 The chloro compound from preparation 269 (101 mg, 0.4 mmol) was added to the amine from preparation 110 (104 mg, 0.45 mmol) in n-butanol (5 ml) containing N,N-diisopropylethylamine (129 μl, 1 mmol) and the mixture was heated under reflux for 2 hours. The reaction mixture was cooled to room temperature and the solid formed was isolated by filtration. The material obtained was dissolved in 5% methanol in dichloromethane and ethereal hydrogen chloride (1M, 2 ml) was added. The solvent

was evaporated under reduced pressure and the residue was dried under vacuum to give the title compound (176 mg).

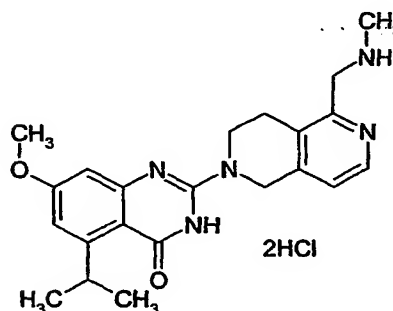
¹H-nmr (DMSO-d₆ 400MHz) δ: 1.19 (d, 6H), 2.77 (s, 3H), 3.00 (m, 4H), 3.34 (t, 2H), 3.47 (m, 2H), 3.83 (s, 3H), 4.40 (m, 3H), 4.91 (s, 2H), 6.81 (s, 1H), 6.90 (d, 1H), 7.50 (m, 2H), 13.38 (s, 1H)

LRMS: m/z (ES⁺) 449 [MH⁺]

Microanalysis: Found: C, 53.26; H, 6.49; N, 14.90; C₂₅H₃₂N₆O 3HCl 0.25H₂O requires; C, 53.39; H, 6.36; N, 14.94%

Example 133

3H-quinazolin-4-one dihydrochloride
5-isopropyl-7-methoxy-2-(5-methylaminomethyl-3,4-dihydro-1H-[2,6]naphthyridin-2-yl)-



The protected amine from preparation 297 (59 mg, 0.12 mmol) was dissolved in dichloromethane (1 ml) and trifluoroacetic acid (1 ml) was added. The reaction mixture was stirred at room temperature for 30 minutes and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ammonium hydroxide and methanol in dichloromethane as eluant (1:7:93). The material obtained was dissolved in dichloromethane and ethereal hydrogen chloride (1M, 1 ml) was added. The solvent was evaporated under reduced pressure and the residue was dried under vacuum to give the title compound as an off white solid (26 mg).

¹H-nmr (DMSO-d₆ 400MHz) δ: 1.19 (d, 6H), 2.63 (s, 3H), 2.98 (t, 2H), 3.84 (s, 3H), 4.15 (t, 2H), 4.30 (s, 2H), 4.41 (m, 1H), 5.12 (s, 2H), 6.80 (s, 1H), 7.26 (d, 1H), 7.55 (s, 1H), 8.46 (d, 1H), 9.26 (s, 1H)

LRMS: m/z (ES⁺) 394 [MH⁺]

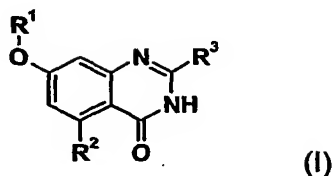
All of the compounds illustrated in examples 1 to 133 display pA2 values versus α 1L (in the method described above) of greater than 7.

Particular compounds of interest display the following pA2 values versus α 1L (in the method described above):

Example Number	pA2 v α 1L
7	9.5
8	9.6
10	9.7
11	10.0
12	9.7
16	9.5
20	9.8
21	10
38	9.5
39	9.6

Claims:

1. A compound of formula (I):

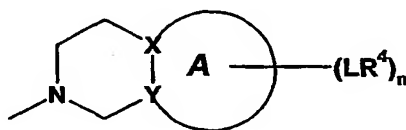


5 or a pharmaceutically acceptable salt or solvate thereof, wherein

R¹ represents C₁₋₄ alkyl;

10 R² represents halo, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyloxy, -SO₂(C₁₋₄ alkyl), C₁₋₄ alkyloxy (optionally substituted by C₃₋₆ cycloalkyl or C₁₋₄ alkoxy), Het or -OHet;

R³ represents a bicyclic group of the formula



15 wherein X and Y are selected from C and N, provided that at least one is C;

Ring A together with X and Y represents a 5- or 6-membered aromatic ring containing 0, 1, 2 or 3 nitrogen atoms in the ring;

20 n is 0, 1 or 2

L independently represents a direct link, C₁₋₄ alkylene or C₁₋₄ alkoxyalkylene;

R⁴ independently represents H, -NR⁵R⁶, C₃₋₆ cycloalkyl, -OR⁷, Het¹ or Het⁴;

25

R⁵ and R⁶ are independently selected from H, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyl-C₁₋₄ alkylene, -SO₂(C₁₋₄ alkyl) and C₁₋₄ alkyl (optionally substituted with -OR⁸, -NR¹⁰R¹¹, Het¹ or Het⁴);

R⁷ is selected from H, C₁₋₄ alkyl, C₁₋₄ alkoxyalkyl, C₃₋₆cycloalkyl, Het² and C₁₋₄alkyl-Het³;

R⁸ is H or C₁₋₄ alkyl;

5

Het, Het¹, Het² and Het³ independently represent a 4 to 7 membered saturated heterocyclic group which may be mono- or bi-cyclic and which contains one or more heteroatoms selected from N, O or S, optionally substituted with OR⁹ and/or C₁₋₄ alkyl optionally substituted by OR⁹;

10

Het⁴ represents a 5 or 6 membered unsaturated heterocyclic group containing one or more heteroatoms selected from N, O or S, optionally substituted with C₁₋₄ alkyl;

R⁹ is H or C₁₋₄ alkyl;

15

R¹⁰ and R¹¹ are independently selected from H and C₁₋₄ alkyl.

2. A compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein

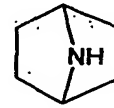
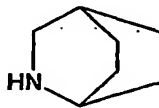
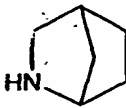
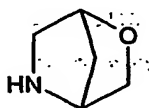
20

Het, Het¹, Het² and Het³ contain at least one N atom and are linked to L through an N atom.

3. A compound of formula (I) according to claim 1 or claim 2, or a pharmaceutically acceptable salt or solvate thereof, wherein

25

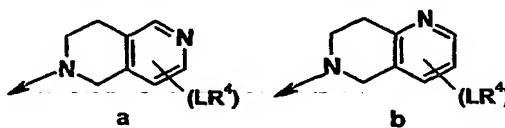
Het, Het¹, Het² and Het³ include azetidine, pyrrolidine, piperidine, piperazine, azepane, morpholine, homomorpholine, or one of the following ring systems



30 optionally substituted by OR⁹, C₁₋₄ alkyl optionally substituted by OR⁹.

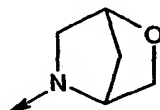
4. A compound of formula (I) according to any of the preceding claims, or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is CH₃.

5. A compound of formula (I) according to any of the preceding claims, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is cyclopropyl.
6. A compound of formula (I) according to any of the preceding claims, or a pharmaceutically acceptable salt or solvate thereof, wherein L represents methylene.
7. A compound of formula (I) according to any of the preceding claims, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 represents a group chosen from a or b (bonded to the quinazolinone through the N-atom as indicated)



where LR^4 is CH_2Het^1 or $CH_2NR^5R^6$ and Het^1 , R^5 and R^6 are as defined in claim 1.

8. A compound of formula (I) according to claim 7, wherein Het^1 is N-linked morpholinyl
9. A compound of formula (I) according to any of the preceding claims, or a pharmaceutically acceptable salt or solvate thereof, wherein R^5 and R^6 are independently selected from H or C_{1-3} alkyl optionally substituted by OCH_3 .
10. A compound of formula (I) according to any of the preceding claims, or a pharmaceutically acceptable salt or solvate thereof, wherein Het , Het^1 , Het^2 and Het^3 are selected from the group comprising pyrrolidine, piperidine, morpholine and



11. A compound of formula (I) as defined in claim 1 selected from:
 5-cyclopropyl-7-methoxy-2-(2-([dimethylamino]methyl)-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone, i.e. example 7;
 5-cyclopropyl-7-methoxy-2-(2-(1-pyrrolidinylmethyl)-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone, i.e. example 8;

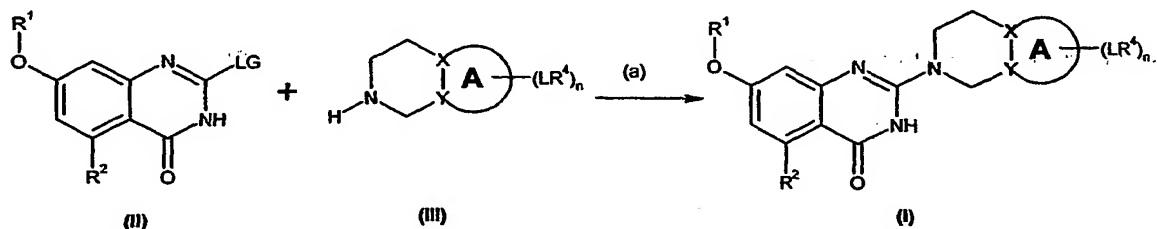
- 5-cyclopropyl-7-methoxy-2-(2-(4-methoxypiperidin-1-yl)methyl)-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone, i.e. example 10;
- 5-cyclopropyl-7-methoxy-2-(2-(4-morpholinylmethyl)-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone, i.e. example 11;
- 5 5-cyclopropyl-7-methoxy-2-(2-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone, i.e. example 12;
- 5-cyclopropyl-7-methoxy-2-(5-[(dimethylamino)methyl]-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone, i.e. example 16;
- 5-cyclopropyl-7-methoxy-2-(5-(4-morpholinylmethyl)-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone, i.e. example 20;
- 10 5-cyclopropyl-7-methoxy-2-(5-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-ylmethyl]-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone, i.e. example 21;
- 5-cyclopropyl-7-methoxy-2-(5-(1-pyrrolidinylmethyl)-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone, i.e. example 38;
- 15 5-cyclopropyl-7-methoxy-2-(5-(1-piperidinylmethyl)-3,4-dihydro[2,6]naphthyridin-2(1H)-yl)-4(3H)-quinazolinone, i.e. example 39;
- and pharmaceutically acceptable salts or solvates thereof.
12. 5-cyclopropyl-7-methoxy-2-(2-(4-morpholinylmethyl)-7,8-dihydro[1,6]naphthyridin-6(5H)-yl)-4(3H)-quinazolinone, or a pharmaceutically acceptable salt or solvate thereof.
- 20
13. A pharmaceutical composition including a compound of the formula (I) as defined in any of claims 1 to 12, or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipient, diluent or carrier.
- 25
14. A compound of the formula (I) as defined in any of claims 1 to 12, or a pharmaceutically acceptable salt or solvate thereof, for use as a medicament.
- 30
15. The use of a compound of the formula (I) as defined in any of claims 1 to 12, or of a pharmaceutically acceptable salt or solvate, in the manufacture of a medicament for the treatment of hypertension, myocardial infarction, male erectile dysfunction, hyperlipidaemia, cardiac arrhythmia, glaucoma and benign prostatic hyperplasia.

16. The use according to claim 15, wherein the treatment is of benign prostatic hyperplasia.

17. A method of treating hypertension, myocardial infarction, male erectile dysfunction, hyperlipidaemia, cardiac arrhythmia and benign prostatic hyperplasia in a mammal, which comprises administering a therapeutically effective amount of a compound of the formula (I) as defined in any of claims 1 to 12, or with a pharmaceutically acceptable salt, solvate or composition thereof, to a mammal in need of such treatment.

18. A method according to claim 17, for treating benign prostatic hyperplasia.

19. A process for the preparation of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, comprising reacting a quinazolinone (II) with an amine (III):



wherein R¹, R², X, Y, LR⁴ and n are as defined in claim 1 and LG represents a leaving group, and where desired or necessary converting the resulting compound of formula (I) into a pharmaceutically acceptable salt or solvate.

20. A compound of formula (II), as defined in claim 19.

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/IB 03/00998

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D401/04 C07D471/04 C07D487/04 A61K31/517 A61P9/12		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) CHEM ABS Data, EPO-Internal		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 23462 A (PFIZER) 3 July 1997 (1997-07-03) cited in the application claims	1,11-19
A	WO 98 30560 A (PFIZER) 16 July 1998 (1998-07-16) cited in the application claims	1,11-19
P, A	WO 02 53558 A (HOFFMAN LA ROCHE) 11 July 2002 (2002-07-11) cited in the application the whole document	1,11-19
<input type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : 'A' document defining the general state of the art which is not considered to be of particular relevance 'E' earlier document but published on or after the international filing date 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) 'O' document referring to an oral disclosure, use, exhibition or other means 'P' document published prior to the international filing date but later than the priority date claimed 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention 'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone 'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. '&' document member of the same patent family		
Date of the actual completion of the international search 11 June 2003		Date of mailing of the international search report 20/06/2003
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016		Authorized officer Francois, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 03/00998

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17,18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Internat	Application No
PCT/IB	03/00998

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9723462	A	03-07-1997	AP 715 A	30-12-1998
			AT 194598 T	15-07-2000
			AU 708979 B2	19-08-1999
			AU 1371997 A	17-07-1997
			BG 102559 A	31-03-1999
			BR 9612263 A	13-07-1999
			CA 2236814 C	18-09-2001
			CZ 9801976 A3	17-03-1999
			DE 69609353 D1	17-08-2000
			DE 69609353 T2	07-12-2000
			DK 877734 T3	20-11-2000
			WO 9723462 A1	03-07-1997
			EP 0877734 A1	18-11-1998
			ES 2151192 T3	16-12-2000
			GR 3034225 T3	29-12-2000
			HR 960616 A1	30-06-1998
			HU 9903560 A2	28-05-2000
			JP 3070958 B2	31-07-2000
			JP 11501668 T	09-02-1999
			NO 982913 A	30-07-1998
			NZ 325248 A	29-09-1999
			PL 327610 A1	21-12-1998
			PT 877734 T	29-12-2000
			SK 81698 A3	10-04-2000
			TR 9801195 T2	21-10-1998
			US 6103738 A	15-08-2000
			US 2002049322 A1	25-04-2002
			ZA 9610784 A	22-06-1998
WO 9830560	A	16-07-1998	AP 819 A	03-04-2000
			AU 724990 B2	05-10-2000
			AU 6208898 A	03-08-1998
			BG 103560 A	30-06-2000
			BR 9807068 A	02-05-2000
			CN 1403453 A	19-03-2003
			CN 1093858 B	06-11-2002
			EA 2851 B1	31-10-2002
			WO 9830560 A1	16-07-1998
			EP 0968208 A1	05-01-2000
			HR 980010 A1	31-10-1998
			HU 0000942 A2	28-04-2001
			JP 3357677 B2	16-12-2002
			JP 2000507966 T	27-06-2000
			NO 993396 A	09-07-1999
			NZ 336302 A	25-08-2000
			PL 334678 A1	13-03-2000
			SK 90799 A3	12-03-2001
			TR 9901604 T2	21-12-1999
			TW 444013 B	01-07-2001
			US 2002040028 A1	04-04-2002
			US 6169093 B1	02-01-2001
			US 6365599 B1	02-04-2002
			ZA 9800166 A	09-07-1999
WO 0253558	A	11-07-2002	WO 02053558 A1	11-07-2002

Form PCT/ISA/210 (patent family annex) (July 1992)

THIS PAGE BLANK (USPTO)

BEST AVAILABLE COPY

THIS PAGE BLANK (USPTO)

BEST AVAILABLE COPY